EXHIBIT 9

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Traumatic Brain Injury (JR Couch, Section Editor)

Current Understanding of Chronic Traumatic Encephalopathy

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Opinion statement

Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative disease found in individuals with a history of repetitive head impacts. The neuropathology of CTE is increasingly well defined. Prospective, longitudinal studies with post-mortem neuropathologic validation as well as in vivo diagnostic techniques are needed in order to advance the understanding of CTE clinically. Given the large number of individuals who incur concussions and other forms of brain trauma, this is an important area for scientific and public health inquiry.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease thought to be associated with a history of repetitive head impacts [1–8, 9••, 10, 11, 12•], such as those sustained through contact sports or military combat. CTE, a distinct neurodegeneration, was first introduced in the literature as "punch drunk" or dementia pugilistica in the early 1900s because of its association with boxing [13]. In fact, much of the

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early literature about the disease focused on the boxing population [1, 13, 14]. However, the disease is found in a more diverse group of individuals with a history of repetitive head impacts including a variety of contact sport athletes, military veterans, domestic abuse victims, and individuals with self-inflicted head banging behavior [7]. Although significant media attention has been brought to this disease, there is relatively little known regarding the pathobiological mechanisms underlying CTE, and a large number of questions remain. The preponderance of the literature has consisted of postmortem neuropathologic assessments with retrospective clinical interviews. As such, the neuropathology of CTE is currently better understood than the clinical presentation or course, and there is a need for prospective longitudinal clinical studies with in vivo diagnostic techniques or neuropathologic validation. This article reviews the current state of our knowledge concerning CTE, including neuropathologic characteristics, clinical features, proposed clinical and pathologic diagnostic criteria, possible risk factors, and future research needs.

Neuropathologic characteristics

Much of the scientific literature on CTE, to-date, is derived from clincopathologic case series of the disease [1–4, 6–8, 9••, 15]. The neuropathology of CTE is increasingly well defined. In 2013, McKee and colleagues published the largest case report to date of individuals with neuropathologically confirmed CTE, presenting proposed criteria for four stages of CTE pathology based on the severity of the findings [9••]. Formal validation of the reliability of these criteria and the staging system are currently being performed by a team of nine neuropathologists, funded by a National Institutes of Health (NIH) U01 grant (1U01NS086659-01, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Biomedical Imaging and Bioengineering (NIBIB); PI, Ann McKee). Detailed criteria of McKee et al.'s pathologic staging criteria can be found in Table 1.

CTE is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles (NFT) beginning perivascularly and at the depths of the cortical sulci. Later stage p-tau pathology becomes more widespread, particularly dense in the medial temporal lobes, also present in the white matter, and leads to prominent neuronal loss and gliosis. The irregular and perivascular nature of the p-tau neurofibrillary tangles, the proclivity for the sulcal depths, and the marked subpial and periventricular involvement are unique features of the disease that distinguish it from other tauopathies. TAR DNA-binding protein 43 (TDP-43) is present in about 80 % of cases. Early stages show sparse TDP-43 positive neurites in cortex, medial temporal lobe, and brainstem. Late-stage pathology presents with TDP-43 intraneuronal and intraglial inclusions in the frontal subcortical white matter and fornix, brainstem, and medial temporal lobe. In most cases of CTE, there are no beta amyloid 1–42 ($A\beta_{1-42}$) positive neuritic plaques. Evidence of axonal injury is common and ranges from multifocal axonal varicosities in earlier stage pathology to severe axonal loss in later stage pathology. Stage I and II CTE can present macroscopically with mild enlargement of the lateral ventricles or third ventricle and/or mild septal abnormalities. Grossly, advanced CTE is characterized by enlargement of the lateral and third ventricles, cavum septum pellucidum, septal perforations, and pallor of the substantia nigra and locus coeruleus. In addition, severe

Table 1. Description of McKee et al.'s (2013) proposed neuropathologic staging of CTE

	Stage I	Stage II	Stage III	Stage IV
P-Tau	Focal perivascular NFTs at depths of cortical sulci	NFTs adjacent to focal epicenters and in nucleus basalis of Meynert and locus coeruleus	Dense in medial temporal lobes and widespread in cortex, diencephalon, brainstem, and spinal cord	P-Tau pathology widespread including in white matter; prominent neuronal loss and gliosis of cortex; hippocampal sclerosis
Macroscopic	Mild lateral ventricle enlargement in some cases	Mild enlargement of the frontal horn of the lateral ventricles or third ventricle in a majority of cases; small cavum septum pellucidum in some cases	Mild cerebral atrophy; enlarged ventricles; depigmentation of locus coeruleus and substantia nigra; septal abnormalities in some cases	Increased cerebral, medial temporal lobe, hypothalamus, thalamus, and mammillary body atrophy; septal abnormalities; enlarged ventricles; pallor of locus coeruleus and substantia nigra
TDP-43	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Severe intraneuronal and intraglial inclusions in cortex, white matter, diencephalon, basal ganglia, brainstem
Axonal Injury	Multifocal axonal varicosities in cortex and subcortical white matter	Multifocal axonal varicosities in cortex and subcortical white matter	Severe axonal loss in cortex and white matter	Severe axonal loss in cortex and white matter
$A\beta_{1-42}$	Present in less than half of subjects with CTE and less than one-third of pure CTE cases. Those with $A\beta_{1-42}$ deposits were significantly older than those without.			

cases may also show profound atrophy of the medial temporal lobes or profound global atrophy. In reports examining former football players [9••] and former boxers [1], the severity of pathology appears to correlate to duration of athletic career. McKee et al. also found an association between severity of pathology to years since retirement from athletics and age at death [9••].

Clinical presentation

Clinical symptoms of CTE generally present years or decades after exposure to trauma [1, 9••, 16••]. Although there are some symptom overlaps between the acute concussive injury and the later-life neurodegenerative process of CTE (eg, attention and concentration loss, headache), it is thought that CTE is distinct from the acute concussion or postconcussion sequelae [17]. That is,

although a history of repetitive brain trauma is thought to be necessary to cause CTE (ie, all neuropathologically confirmed cases of CTE to date have had a history of repetitive brain trauma), CTE symptoms are not just the cumulative effects of this process. Furthermore, there is no clear relationship between prolonged acute concussion symptoms (eg, postconcussion syndrome) and the pathology of CTE.

Evidence to-date suggests that CTE presents clinically with symptoms in one or more of four possible domains: mood, behavior, cognition, and motor [9••, 16••]. Commonly noted mood features include depression, irritability, and hopelessness. Behavioral features may include impulsivity, explosivity, and aggression. Cognitive features can include memory impairment, executive dysfunction, and in severe cases dementia. Motor features, including parkinsonism, ataxia, and dysarthria, appear in a subset of cases, predominantly boxers. In addition, chronic headache is also experienced in some cases [7, 9••, 15, 18, 16••, 19, 20•, 21•]. Two distinct clinical presentations of CTE have been described in a recent study by Stern et al., substantiating evidence from earlier literature regarding this possibility [1, 16••, 22–24] According to Stern and colleagues, the first type of clinical presentation initially presents with mood and behavioral symptoms earlier in life (mean age approximately 35) and progresses to include cognitive symptoms later in the disease course. The second clinical presentation begins with cognitive impairment later in life (mean age approximately 60), which may progress to include mood and behavioral symptoms [16••].

Earlier cases of CTE tended to report a higher prevalence of motor features than more recent reports. Differences in symptom profile have led some researchers to differentiate "classic" and "modern" CTE clinically [25•]. It is worth noting that "classic" cases were predominantly boxers, whereas more recent descriptions have been dominated by football players. Differences in the nature of exposure could account for differences in presentation— biomechanical comparisons of head impact dynamics in boxing and football have shown that boxers experience proportionally more rotational acceleration than in football [26, 27]. Further, computational modeling of boxing impacts suggests that stress in boxing impacts is greatest on midbrain structures, and midbrain damage may account for the parkinsonian features found in CTE [27, 28]. Supporting this theory, in the case series of neuropathologically confirmed CTE by McKee and colleagues [9••], professional boxers and professional football players with neuropathologically confirmed CTE, professional boxers exhibited significantly more motor symptoms (eg, ataxia dysarthria) relative to football players. This clinical difference between boxers and football players was mirrored in the pathology: boxers displayed more cerebellar scarring than football players. Thus, although there is a notable difference in the presence of motor symptoms between the earlier and more recent CTE literature, this may be attributable, at least in part, to the variance in head impact exposure types experienced by boxers and football players.

The question of suicide in CTE remains contentious [29•]. Several CTE case series have included victims of suicide.[6, 7, 9••, 16••] However, our lack of understanding of the population incidence of CTE limits our ability to attribute a complex and multifactorial behavior such as suicide to underlying CTE proteinopathy. The issue is further complicated considering that well

established risk factors for suicide and suicidal ideation such as substance use and depression [30, 31] are often comorbid in cases of CTE [9••, 16••]. The current literature does not provide means to separate the contribution (or lack thereof) of these different potential factors to the act of completing suicide. Further, premature association between repetitive brain trauma and suicidality could result in a 'self-fulfilling prophecy' prompting wider suicides in exposed individuals irrespective of contribution (or noncontribution) from CTE symptoms. Available scientific evidence cannot wholly support the notion that CTE *causes* suicidal thoughts or behaviors, and such assumptions or assertions should be avoided without further evidence.

All efforts to define the clinical presentation of CTE are also limited due to the lack of in vivo diagnosis and use of retrospective reviews of case reports[15, 20•, 21•] or family interviews [9••, 16••]. This information is valuable to determine initial correlations between presence of neuropathology and clinical manifestation; however, because of their retrospective third-party nature, there are significant limitations to these data. Although some of the earlier literature includes clinical evaluations [13, 32], the findings and their generalizability is limited by the technology of the era [25•]. Increased prospective and longitudinal clinical research in this area is critically needed.

Clinical diagnosis and in vivo biomarkers

Several important studies are underway to develop reliable biomarkers for CTE during life, although like most neurodegenerative diseases, the definitive diagnosis of CTE is based on neuropathologic examination. To date, three groups of authors have proposed preliminary clinical and/or research diagnostic criteria [20•, 21•, 33•]. The three independently proposed criteria are largely comparable and follow a structure similar to the National Institutes on Aging—Alzheimer's Association clinical diagnostic criteria [34] by differentiating between probable and possible cases based on endorsement of various signs and symptoms. All criteria require a patient to have a history of brain trauma, and to exhibit symptoms consistent with the clinical presentation of CTE described in the literature that could not likely be explained by another condition. All three criteria identified behavioral and cognitive disturbances as important for a diagnosis of CTE. Research groups differ concerning the importance of motor features; Jordan has suggested that motor features resulting from injury to the pyramidal tracts, extrapyramidal system, and cerebellum are necessary for CTE, whereas both Montenigro et al. and Victoroff have suggested a less central role of motor features in diagnosing clinical CTE [20•, 21•, 33•]. Montinegro et al. suggested codifying the clinical syndrome associated with repetitive brain trauma as Traumatic Encephalopathy Syndrome (TES), and reserving CTE for postmortem neuropathologic diagnoses [33•]. In order to confirm the utility of these criteria in either research or clinical settings, future studies will need to demonstrate an ability to reliably differentiate between cases and noncases with a high degree of specificity. A comparison of these proposed criteria can be found in Table 2.

Table 2. Description of existing proposed research or clinical diagnostic criteria for CTE

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
Disease/disorder	CTE	Traumatic encephalopathy syndrome (TES), a clinical syndrome associated with history of repetitive brain trauma	CTE
Subclassifications	Definite, Probable, Possible, Improbable	behavioral/mood variant (BMv), cognitive variant (COGv), mixed variant (MIXv), dementia (D); differentiated depending on the presence of motor features or clinical course, or probable, possible, or unlikely CTE based on biomarkers.	Clinically probable, Clinically possible; acute onset, delayed onset; apparently persistent, apparently progressive, apparently improving.
History of brain trauma	No specific guidance as to the specific type or amount of brain trauma required.	History of multiple head impacts (mTBI, TBI, or subconcussive trauma) from high exposure contact sports, other significant exposure to repetitive hits, or any activity resulting in TBI.	Probable or definite exposure to one or more of the following: TBI, concussion, subconcussion.
Duration of symptoms	No guidance provided.	Symptoms must be present for a minimum of 12 months.	Symptoms must last for at least two years after impact.
onset of symptoms	Typically manifest later in life after a period of latency.	Symptom onset must be delayed by at least 2 years from exposure to brain trauma.	*Acute onset* cases have no period of recovery in the 6–12 months following concussion. *Delayed onset* cases have evidence of decline following apparent recovery post-impact.
Differential diagnosis	*Definite* (neuropathologically confirmed) and *Probable* cases of CTE involve ruling out of other possible neurological causes. *Possible* CTE can potentially be explained by other known neurological causes. *Improbable* CTE can be explained by a pathophysiological process unrelated to brain trauma.	Must rule out other neurological disorders, including residual symptoms from acute TBI or postconcussion syndrome that could account for symptoms. Comorbidities such as substance use, other neurodegenerative diseases can be present.	Must rule out other medical or psychiatric diagnosis that could explain symptoms.
Clinical features	*Behavioral and psychiatric features:* aggression or agitation, apathy, impulsivity, depression, delusions, suicidality.	*Core clinical features:* Difficulties in cognition substantiated with scores of ≥1.5 SD below norms on standardized mental status	*Symptoms:* headache, speech changes, tremor, deterioration in stance or gait, falls, cognitive decline, mood changes, anxiety

Table 2. (Continued)

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
	Cognitive features: impaired attention and concentration, memory problems, executive dysfunction, dementia, visuospatial difficulties, language impairment. *Motor features:* dysarthria, spasticity, ataxia, parkinsonism, gait disturbance, motor neuron disease (possibly).	or neuropsychological tests; behavior issues (eg, short fuse, violence); mood disturbance (eg, depression). *Supportive features:* impulsivity, anxiety, apathy, paranoia, suicidality, chronic headache, motor signs (eg, parkonsinism), documented functional decline, delayed onset. Potential Biomarkers for Diagnosis of Probable CTE: cavum septum pellucidum, normal beta amyloid CSF levels, elevated CSF p-tau/tau ratio, negative amyloid imaging, positive tau imaging, cortical atrophy based on neuroimaging, cortical thinning based on neuroimaging.	paranoia, personality change (eg, irritability, apathy), alcohol abuse dependence or sensitivity, anger or aggression. *Neurological signs:* nystagmus, dysarthria, reduced facial expression, hypertonia or rigidity, hyperreflexia, hemiparesis, tremor, limb ataxia, disorders of gait or stance. *Neurobehavioral signs:* memory loss, other cognitive impairment (eg disorientation, confusion), mood disturbance (eg depression), thought disorder, pathological personality traits (eg, irritability, apathy), anger or aggression.
Symptom requirements for diagnosis	*Definite:* neurological process consistent with clinical presentation of CTE along with pathological confirmation. *Probable:* two or more of the following conditions: cognitive and/or behavioral impairment, cerebellar dysfunction, pyramidal tract disease or extrapyramidal disease; distinguishable from other disease processes and consistent with the clinical presentation of CTE. *Possible:* neurological process consistent with clinical presentation of CTE but potentially explained by other neurological disorders. *Improbable:* inconsistent with clinical description of CTE and be explained by a process unrelated to brain trauma.	At least one core clinical feature must be present and considered a change from baseline functioning, at least two supportive features must be present. *TES-BMv:* behavioral and/or mood core features without cognitive core features. *TES-COGv:* cognitive core features without behavioral and/or mood core features. *TES-MIXv:* both cognitive core features and behavioral and/or mood core features. *TES-D:* progressive course of cognitive core features, evidence of functional impairment. *Probable CTE:* meets TES criteria, progressive, >1 positive CTE biomarker. *Possible CTE:* meets TES criteria, either has not undergone biomarker testing or has had a negative biomarker (other than tau imaging) or has another disorder that may account for presentation. Unlikely CTE: does not meet TES criteria and/or has had negative tau imaging.	*Clinically* probable diagnosis requires at least two symptoms and three signs. Clinically possible diagnosis requires at least one symptom and two signs. Cases should be identified as acute onset or delayed onset. (See onset of symptoms above.) Cases should be identified as either apparently persistent (clinical features last more than two years), apparently progressive (clinical features last for more than two years and are unequivocally progressing), or apparently improving.

CTE chronic traumatic encephalopathy.

To date, there are no objective, validated in vivo biomarkers of CTE. However, important work in the area of CTE biomarkers is currently underway. Several research groups[18, 21•, 35•, 36] have suggested that negative amyloid PET imaging in the presence of positive tau PET imaging could provide a reliable way to differentiate between cases of CTE and Alzheimer's disease (AD). Small and colleagues published preliminary findings in a study of five former professional football players using the PET ligand ^{18}F-FDDNP, which binds to both tau and amyloid [35•, 37]. Although they suggested that positive findings (higher signals) using this technology could be indicative of underlying CTE pathology, the nonspecific binding of ^{18}F-FDDNP means that the signal cannot be solely attributed to the presence of tau. Thus, neuropathologic confirmation is needed to determine the underlying pathology. Alternatively, a tau-specific PET ligand, such as those in preliminary studies by Chien et al. [38••], may be used to measure tau in vivo as a potential biomarker for CTE. Preliminary work using diffusion tensor imaging has shown evidence of persistent changes in white matter integrity after periods of head impact exposure [39•, 40•], which may prove useful in distinguishing CTE. Magnetic resonance spectroscopy (MRS), a method of measuring brain metabolites, has shown promise in preliminary studies by Lin and colleagues [41•]. Cerebrospinal fluid (CSF) markers have been useful in the AD diagnostic process [34] and CSF p-tau levels have been shown to correlate with levels of p-tau NFT deposition in the brain [42]. Thus, CSF protein measures may useful biomarkers for CTE, and in the differentiation of CTE from other neurodegenerative diseases.

Risk factors

As stated above, to-date, all individuals with neuropathologically confirmed CTE have a history of repetitive head impacts. Although this type of exposure seems to be *necessary* for the occurrence of CTE, it does not appear to be *sufficient*. That is, not all individuals with a history of repetitive head impact exposure get CTE. As previously noted, detailed relation between head impact exposure (eg, frequency, magnitude, age of first exposure) and later-life neurologic outcomes is not well understood. To date, other risk factors for CTE, beyond head impact exposure, are unknown.

Genetics

Genetic risk factors may play a role in development of CTE. The apolipoprotein (ApoE) ε4 allele is the most powerful predictor of sporadic AD [43]. There have been several reports linking the ApoE ε4 allele and head injury with a variety of negative outcomes, including prolonged recovery and poor cognitive performance [44–47]; however, these studies lacked neuropathologic disease confirmation of disease. Findings in neuropathologically confirmed studies are mixed. In the series studied by Stern et al. [16••] and McKee et al. [7], there was an overrepresentation of ε4 carriers in a cohort of neuropathologically confirmed CTE relative to population norms. However, in a study with a larger sample size (N=103), the effect failed to reach significance [9••]. While early clinical findings established a link between clinical outcomes and APOE ε4

expression, the literature has not definitively established a link between APOE genotype and CTE pathology. Future research should examine the association between APOE genotype and CTE, as well as other possible genetic risk factors for CTE such as the MAPT gene or the TARDBP gene.

Lifestyle

One important challenge to accurately describing the clinical presentation and course of CTE are the lifestyle comorbidities associated with contact sport athletes and military veterans, in whom the disease has been most studied. Comorbidities such as alcohol abuse or dependence, recreational drug use, and performance enhancing drug use can all lead to personality changes and neuropsychiatric difficulties [48–51]. A non-negligible portion of individuals with neuropathologically confirmed CTE have had reported substance abuse [16••]. However, there are neuropathologically confirmed cases of CTE without a history of any of these afflictions, indicating that they are not causative factors. Therefore, understanding whether and to what extent lifestyle issues, such as those noted, influence the clinical manifestations of CTE is necessary.

Conclusions

Both in CTE and other neurodegenerative diseases, neuropathologic abnormalities are not always directly correlated with specific clinical signs and symptoms. There are likely other factors that influence disease occurrence, progression, and clinical presentation. To date, our understanding of the clinical presentation of CTE is heavily reliant on retrospective interviews with family members of individuals with neuropathologically confirmed CTE. Currently, our neuropathologic understanding of CTE is based on a biased sample of individuals who are who are predominantly among those most exposed to repetitive head impacts (eg, professional football players, professional boxers). What we understand less well is how repetitive head impacts from other less severe and less predictable exposures, such as the occasional concussion or fall, may or may not relate to the development of CTE. However, despite these limitations, there is sufficient scientific evidence to reasonably conclude that CTE is a distinct pathology that is caused, at least in part, by repetitive head impacts.

Our understanding of CTE has progressed considerably in the last several years. However, important gaps still exist in our understanding such as the incidence and prevalence of CTE, nonhead trauma risk factors for the disease, and in vivo diagnostic techniques. There are a variety of factors beyond a history of repetitive head impacts (eg, personality, lifestyle) that differentiate collegiate or professional contact sport athletes from the general public. Understanding to what extent these other factors influence clinical signs and symptoms is critical. Furthermore, there are other non-CTE results of repetitive head impacts. For example, in a 2012 study by Lehman et al. retired NFL athletes were found to have a neurodegenerative mortality rate three-times that of the U.S. population generally, and when AD and amyotrophic lateral sclerosis were examined specifically NFL mortality rates were four times that of the general population [52••]. Differentiating the clinical manifestations of CTE and non-CTE results of head impacts is needed. In order to facilitate clinical understanding of CTE, the most

pressing issue we are faced with is developing an in vivo diagnostic tool. With an in vivo diagnosis, we could begin to directly assess clinical symptomatology and progression, research incidence and prevalence in a living population, and begin therapeutic studies. Without an in vivo diagnosis, the questions we can accurately address are limited by the methodologies we are able to employ.

As CTE research has a particular ability to be misunderstood by the lay public and sensationalized in the media, caution needs to be exercised when discussing results of scientific studies and generalizing the results to the population as a whole. Many individuals have some history of head impacts incurred through sports participation or other activities [53]. However, the pathophysiological mechanism linking this initial trauma, whether concussive or subconcussive, to later-life CTE pathology has yet to be elucidated. Furthermore, without a more complete understanding of the incidence, prevalence, and possible risk factors that lead to the development of CTE, it is impossible for the general population to accurately assess their risk of CTE. Unfortunately the popular media, which has reported on CTE because of its association with professional athletics, often does not present findings with the same accuracy, caution, or contextualization as the original peer-reviewed scientific publications. In order to avoid causing undue panic in individuals who have a history of concussions or other traumatic brain injuries, the scientific community and the media need to clearly address the considerable gaps that exist in our understanding of CTE [54].

Compliance with Ethics Guidelines

Conflict of Interest

Christine M. Baugh and Clifford A. Robbins declare that their institution has received R01 grant support from the NIH. Robert A. Stern declares that his institution has received R01 grant support from the NIH. Dr. Stern also declares the receipt of consulting fees from Athena Diagnostics, as well as gifts to his institution from the National Football League, the Andlinger Foundation, and the NFL Players Association. Dr. Stern also receives royalties from Psychological Assessment Resources, Inc., for psychological tests developed, and he has received consulting fees from law firms in cases involving sports-related brain trauma. Ann C. McKee declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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EXHIBIT 10

Montenigro et al. Alzheimer's Research & Therapy 2014, 6:68
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alzheimer's research&therapy

REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

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Abstract

The long-term consequences of repetitive head impacts have been described since the early 20th century. Terms such as punch drunk and dementia pugilistica were first used to describe the clinical syndromes experienced by boxers. A more generic designation, chronic traumatic encephalopathy (CTE), has been employed since the mid-1900s and has been used in recent years to describe a neurodegenerative disease found not just in boxers but in American football players, other contact sport athletes, military veterans, and others with histories of repetitive brain trauma, including concussions and subconcussive trauma. This article reviews the literature of the clinical manifestations of CTE from 202 published cases. The clinical features include impairments in mood (for example, depression and hopelessness), behavior (for example, explosivity and violence), cognition (for example, impaired memory, executive functioning, attention, and dementia), and, less commonly, motor functioning (for example, parkinsonism, ataxia, and dysarthria). We present proposed research criteria for traumatic encephalopathy syndrome (TES) which consist of four variants or subtypes (TES behavioral/mood variant, TES cognitive variant, TES mixed variant, and TES dementia) as well as classifications of 'probable CTE' and 'possible CTE'. These proposed criteria are expected to be modified and updated as new research findings become available. They are not meant to be used for a clinical diagnosis. Rather, they should be viewed as research criteria that can be employed in studies of the underlying causes, risk factors, differential diagnosis, prevention, and treatment of CTE and related disorders.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by the accumulation of hyperphosphorylated tau protein (p-tau) in neurons and astrocytes in a pattern that is unique from that of other tauopathies, including Alzheimer's disease (AD) and frontotemporal lobar degeneration. The p-tau deposition initially occurs focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci. It spreads to involve superficial layers of adjacent cortex, eventually resulting in widespread degeneration of the medial temporal lobes, frontal lobes, diencephalon, and brainstem [1,2]. Unlike AD, there is a paucity of beta amyloid neuritic plaques. CTE has been found most often in professional athletes involved in contact sports (for example, boxing and American football) who have been subjected to repetitive head blows resulting in concussive and subconcussive trauma [3,4]. Neuropathologically confirmed CTE has been reported in individuals as young as 17 and in athletes who played sports only through high school or college. It also has been found in non-athletes who have experienced repetitive head impacts, including epileptics, developmentally disabled individuals who head-bang, and victims of physical abuse [2]. Moreover, CTE has been neuropathologically diagnosed in military service members previously deployed in Iraq and Afghanistan with histories of repetitive brain trauma [2,5]. At this time,

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it is not completely clear whether all cases of neuropathologically confirmed CTE would demonstrate a progressive course if they lived long enough.

All cases of neuropathologically confirmed CTE reported to date have had a history of repetitive head impacts, although there has been some suggestion that a single traumatic brain injury (TBI) may also lead to the neuropathological changes of CTE [6]. Although head impacts appear to be necessary for the initiation of the pathogenetic cascade that eventually leads to neurodegeneration, the history of head impacts is not sufficient and additional risk factors (including genetic susceptibility markers) remain unknown. The incidence and prevalence of CTE are also unknown, although the number potentially affected could be quite large. Every year, between 1.6 and 3.8 million individuals in the US experience a sports-related concussion [7], and the number of youth sports-related concussions has grown in recent years [8]. The incidence of repetitive subconcussive blows (that is, hits to the head that produce enough force to hamper neuronal integrity but that do not result in clinical concussion symptoms) is much greater [9]. For example, a study by Broglio and colleagues [10] found that, per season, high school football players receive an average of 652 head blows that exceed 15 g of force. With over 1 million high school students playing American football each year and with the size and speed of football players increasing [11], the public health impact of CTE may be quite significant in future years.

In vivo diagnosis of CTE is needed to conduct research on risk factors and epidemiology and to perform clinical trials for prevention and treatment. Sensitive and specific biomarkers for CTE are being developed and include structural and neurochemical imaging techniques and positron emission tomography (PET) with new ligands that selectively bind to p-tau [4,12,13]. These approaches hold promise to detect underlying neuropathological changes of CTE. However, the clinical features directly associated with these changes have only recently been described and have been based on retrospective reports of family members of deceased individuals who received a neuropathological diagnosis of CTE [2,14].

In a recent article from our group [14], we examined the clinical presentation of 36 adult males selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy Brain Bank. The cases were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had family member informants who provided retrospective reports of history and clinical features. The semi-structured 'psychological autopsies' were conducted blind to the subjects' neuropathological findings. Three of the 36 subjects were asymptomatic. In the remaining 33 symptomatic subjects, a triad of cognitive, behavioral, and mood impairments was found, and cognitive changes were reported for almost all subjects at some time in the course of disease. However, two relatively distinct clinical presentations emerged: one group had initial features involving behavior (that is, explosivity, physical and verbal violence, being 'out of control', and impulsivity) or mood (that is, depression and hopelessness) or both (n = 22), and another group had initial features involving cognition (that is, episodic memory impairment, executive dysfunction, poor attention, and concentration) (n = 11). Symptom onset for the 'behavior/mood group' occurred at a significantly younger age than for the 'cognition group'. Most subjects in the behavior/mood group eventually developed cognitive difficulties, although significantly fewer subjects in the cognition group eventually demonstrated behavioral and mood changes. Significantly more subjects in the cognition group developed dementia than those in the behavior/mood group. Less than one third of the sample had reported motor features, including parkinsonism.

Although the study by Stern and colleagues [14] involved the largest case series to date of neuropathologically confirmed cases of CTE without comorbid conditions and with clinical histories, the sample size was small and the generalizability of the findings was hampered by the potential bias of a sample composed of former athletes whose family members agreed to their brain donation. This limitation notwithstanding, the finding of two possible clinical subtypes of CTE was consistent with previous literature. In the present article, we provide a review of the world's literature on the clinical features exhibited by athletes with histories of repetitive head impacts. After the literature review, we provide proposed research diagnostic criteria for 'traumatic encephalopathy syndrome' (TES), derived from this literature review and from our own research into the clinical presentation of CTE [1,2,14]. As described below, these criteria are meant to initially characterize what is known to date and provide a foundation for developing more precise clinical criteria informed by ongoing and future research and clinical review.

Historical terms for chronic traumatic encephalopathy

In his seminal 1928 article in the *Journal of the American Medical Association*, Martland [15] used the term 'punch drunk' to describe boxers suffering from symptoms he believed to be related to the repetitive blows they received in the ring. Since that time, various terms have been used to describe the clinical syndrome associated with repetitive head impacts, predominantly in studies of boxers. In 1934, Parker [16] published an article in which he referred to the 'traumatic encephalopathy of pugilists'. In 1937, Millspaugh [17] first used the term 'dementia pugilistica', which is still used by clinicians and researchers. Other

terms coined through the decades include 'traumatic encephalitis' [18], 'cumulative encephalopathy of the boxer' [19], 'psychopathic deterioration of pugilists' [20], 'chronic boxer's encephalopathy' [21], and 'traumatic boxer's encephalopathy' [22]. In 1949, Critchley first used the designation 'chronic traumatic encephalopathy' [23], or CTE, but later modified it to 'chronic progressive traumatic encephalopathy' [24] because several cases apparently progressed from an early mild state to severe dementia [23-25]. Johnson [26] suggested that the latter term erroneously implies that progression is inevitable. In his case series, little to no deterioration is reported in half of the cases followed for 5 years. In recent reviews of the literature, Victoroff (alone [27] and with Baron [28]) suggested using the more general and inclusive term 'traumatic encephalopathy'.

In 2005, Omalu and colleagues [29] described the first case of neuropathologically confirmed CTE in an American football player. Since that time, there has been increasing public attention to this disease, and reports of CTE in deceased football players, including several well-known athletes, have prompted a tremendous focus on what is commonly referred to as football's 'concussion crisis'. The scientific community also has become dramatically more aware of CTE since it was discovered in American football players. For example, a PubMed search using the terms 'chronic traumatic encephalopathy', 'traumatic encephalopathy', 'dementia pugilistica', or 'punch drunk' resulted in 14 publications in the 5-year period ending in December 2001 compared with 116 publications in the 5-year period ending in December 2013.

Early concepts regarding subtypes

In a 1950 editorial in the *British Medical Journal*, Jokl [30] stressed that CTE was not a single syndrome but rather two kinds of chronic impairment, with either predominant 'behavioral-psychopathic or neurological-psychiatric' features. He described the behavioral-psychopathic subtype as involving 'viciousness', 'murder committed from jealousy', and delinquency. In contrast, he described the neurological-psychiatric subtype as involving cognitive deficits, dementia, and motor impairment [30-32]. Grahmann and Ule [33] (1957) described three general subtypes: (1) a progressive dementia that typically involved cognitive impairment and developed following a latency from the time of boxing retirement, (2) a stable neurological presentation temporally and etiologically related to the head impacts and not representative of a progressive disease, and (3) a paranoid and psychotic subtype absent of cognitive changes. Critchley [23] maintained that there were three commonly recurring presentations of CTE that resembled, but could be distinguished from, (1) neurosyphilis (for example, psychopathy, altered personality, and later dementia), (2) multiple sclerosis (for example, scanning speech, tremor, and progressive cognitive decline), and (3) frontal lobe tumor (for example, executive impairments, headache, and eye ache). He later added a fourth presentation: striatal parkinsonian (for example, masked facial features and tremor) [24]. In a study of 17 retired boxers, Johnson [26] described four different 'organic psychosyndromes': cognitive problems with progressive dementia, behavioral issues related to 'morbid jealousy', behavioral issues related to rage and personality disorders, and mood and behavioral disturbance related to persistent psychosis.

Literature search methods

To examine previous literature describing the clinical presentation of CTE associated with exposure to head impacts through sports participation, we conducted a literature search using PubMed, PubMed Central, and Medline databases. Search terms included 'chronic traumatic encephalopathy', 'punch drunk', 'traumatic encephalopathy', 'dementia pugilistica', 'chronic boxer's encephalopathy', 'chronic progressive traumatic encephalopathy', 'psychopathic deterioration of pugilists', and 'repetitive brain injury'. In addition, bibliographies of recent literature reviews were cross-referenced [1,27,34-39]. It should be noted that most online databases are limited to articles published since the 1950s. Because essential work in this field began in 1928, archival research was carried out by hand, and international works were obtained with assistance from the Boston University Medical Library Interlibrary Loan Department. Materials retained included articles, reviews, dissertations, society transactions, association reports, and book chapters. To be reasonably confident about the diagnoses used, several criteria were used to determine inclusion in this review: (1) only case series, and not individual case reports, were included; (2) adequate information must be provided in the report to allow classification of cases as confirmed CTE, probable CTE, or possible CTE by using Jordan's criteria [35,40,41]; and (3) only cases involving athletes were included.

Results of literature review

Following the exclusion of articles and cases that did not meet the above criteria, the literature review resulted in 202 cases from 20 published case series, four books, and one medical dissertation. The cases are summarized in Table 1 [2,16,22-26,29,31-33,42-54]. Nineteen cases were published before 1950, 29 cases were published in the 1950s, 49 were published in the 1960s, 13 were published in the 1970s, four were published in the 1980s, 19 were published in the 1990s, and 69 were published since 2000. Using Jordan's criteria [35], we approximated that 29 would have possible CTE, 90 would have probable CTE, and 83 would have definite CTE. Of the entire sample, 141 were boxers, 54 were American football players, five

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy

Study	Sample (total n = 202)	Clinical features			
		Behavioral	Mood	Cognition	Motor
Parker [16] (1934)	Boxers (n = 3)	Social inappropriateness	Anxiety	Reduced intelligence	Ataxia
			Labile emotions	Memory impairment	Clonus
		Childish behavior	Fatigue	Impaired attention	Dragging gait
				Visuospatial difficulties	Dysarthria
					Muscle weakness
					Spasticity
					Tremor
Herzog [42] (1938)	Boxers (n = 7)	Boastfulness	Apathy	General cognitive impairment	Dysarthria
		Personality changes	Flat affect	Memory difficulties	Masked facies
		Impulsiveness		Perseveration	Shuffling gait
		Loss of control		Language difficulties	Truncal ataxia
				Alogia	
				Dementia	
Knoll *et al.* [43] (1938)	Boxers (n = 3)	Personality changes	Apathy	General cognitive impairment	Ataxia
			Flat affect	Memory impairment	Dysarthria
			Loss of interest	Visuospatial difficulties	Masked facies
			Prolix	Alogia	
				Dementia	
Jokl [31] (1941) and Jokl and Guttmann [32] (1933)	Boxers (n = 3)	Boastfulness	Apathy	Reduced intelligence	Ataxia
		Childish behavior	Depression	Executive dysfunction	Dysarthria
		Paranoid delusions	Euphoria	Memory impairment	Masked facies
		Personality changes	Fatigue	Impaired attention	Muscle weakness
		Physical violence	Flat affect	Altered concentration	Shuffling gait
		Psychosis	Insomnia	Language difficulties	Tremor
		Short fuse	Irritability	Dysgraphia	Unsteady gait
		Explosivity	Labile emotions	Visuospatial difficulties	
		Social inappropriateness	Loss of interest		
		Verbal violence	Mania		
			Mood swings		
Schwarz [44] (1953)	Boxers (n = 3)	Personality changes	Fearfulness	Memory impairment	Ataxia
		Short fuse	Irritability	Altered concentration	Dysarthria
		Explosivity	Labile emotions	Language difficulties	Masked facies
					Muscle weakness
					Stamping gait
					Tremor
					Unsteady Gait
Soeder and Arndt [45] (1954)	Boxers (n = 5)	Boastfulness	Apathy	General cognitive impairment	Clonus
		Disinhibited behavior	Depressed mood	Executive dysfunction	Dysarthria
		Inappropriate speech	Euphoria	Memory impairment	Masked facies
		Paranoia	Fatigue	Impaired attention	Rolling gait
		Personality changes	Flat affect	Altered concentration	Tremor
		Physical violence	Insomnia	Language difficulties	Truncal ataxia

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy *(Continued)*

		Psychosis	Mania	Alogia	Unsteady gait
		Short fuse	Mood swings		
		Explosivity	Prolix		
		Social inappropriateness			
Grahmann and Ule [33] (1957)	Boxers (n = 4)	Childish behavior	Apathy	General cognitive impairment	Dysarthria
	Confirmed CTE (1)	Disinhibited behavior	Depressed	Executive dysfunction	Swaying gait
		Disinhibited speech	Euphoria	Memory impairment	Masked facies
		Impulsivity	Labile emotions	Impaired attention	
		Loss of control	Fatigue	Altered concentration	
		Physical violence	Flat affect	Dementia	
		Personality changes	Irritable		
		Short fuse	Mood swings		
		Explosivity	Prolix		
		Social inappropriateness			
Muller [46] (1958)	Boxers (n = 3)	Social isolation	Fatigue	General cognitive impairment	Dysarthria
		Personality changes	Irritability	Executive dysfunction	Unsteady gait
		Lack of insight		Impaired attention	Spastic gait
				Memory impairment	
				Altered concentration	
				Dementia	
Spillane [47] (1962)	Boxers (n = 5)	Childish behavior	Anxiety	General cognitive impairment	Ataxia
		Disinhibited behavior	Depressed mood	Reduced intelligence	Dysarthria
		Impulsivity	Euphoria	Memory impairment	Dragging gait
			Mania	Visuospatial difficulties	Muscle weakness
			Payne mood swings	Dysgraphia	Tremor
				Lack of insight	Unsteady gait
				Dementia	
Mawdsley and Ferguson [22] (1963)	Boxers (n = 10)	Impulsivity	Apathy	General cognitive impairment	Ataxia
		Loss of control	Depression	Reduced Intelligence	Dysarthria
		Physical violence	Insomnia	Memory impairment	Dragging gait
		Psychosis	Irritability	Language difficulties	Masked facies
		Paranoid delusions		Dysgraphia	Muscle weakness
		Personality changes		Dementia	Tremor
		Short fuse			Unsteady gait
		Explosivity			
		Social inappropriateness			
		Verbal violence			
Critchley [23-25] (1949, 1957, 1964)	Boxers (n = 17)	Disinhibited speech	Depressed	General cognitive impairment	Ataxia
		Disinhibited behavior	Labile emotions	Reduced intelligence	Clumsy
		Impulsivity	Euphoria	Memory impairment	Dysarthria
		Lack of insight	Insomnia	Impaired attention	Masked facies
		Physical violence	Irritable	Altered concentration	Muscle weakness
		Personality changes	Loss of interest	Visuospatial difficulties	Tremor
		Social inappropriateness	Fatigue	Dementia	Unsteady gait
		Short fuse			

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy *(Continued)*

Payne [48] (1968)	Boxers (n = 6)	Disinhibited behavior	Depressed mood	General cognitive impairment	Ataxia
		Impulsivity	Labile emotions	Reduced intelligence	Dysarthria
		Paranoid delusions	Insomnia	Altered concentration	Unsteady gait
		Physical violence	Mania	Visuospatial difficulties	
		Psychotic	Mood swings	Memory impairment	
		Verbal violence	Suicidal ideation		
Johnson [26] (1969)	Boxers (n = 17)	Loss of control	Anxiety	General cognitive impairment	Ataxia
		Paranoid delusions	Labile emotions	Reduced intelligence	Dysarthria
		Personality changes	Irritability	Memory impairment	Tremor
		Psychotic		Dementia	Dragging gait
		Short fuse			Masked facies
		Explosivity			Muscle weakness
		Verbal violence			
Roberts [49] (1969)	Boxers (n = 11)	Lack of insight	Apathy	Reduced intelligence	Ataxia
		Paranoid delusions	Depression	Executive dysfunction	Dysarthria
		Psychosis	Euphoria	Memory impairment	Dragging gait
		Short fuse	Flat affect	Perseveration	Masked facies
		Explosivity	Labile emotions	Impaired attention	Muscle weakness
				Altered concentration	Shuffling gait
				Language difficulties	Spasticity
				Dysgraphia	Tremor
				Visuospatial difficulties	Unsteady gait
				Dementia	
Corsellis *et al.* [50] (1973)	Boxers (n = 13) Confirmed CTE (13)	Childish behavior	Anxiety	General cognitive impairment	Ataxia
		Paranoid delusions	Labile emotions	Reduced intelligence	Dysarthria
		Personality changes	Irritability	Memory impairment	Masked facies
		Short fuse		Dementia	Muscle weakness
		Explosivity			Tremor
		Social inappropriateness			Staggering gait
		Social isolation			Shuffling gait
		Verbal violence			Unsteady gait
Sabharwal *et al.* [51] (1987)	Boxers (n = 4)	Inappropriate speech	Depression	Reduced intelligence	Ataxia
			Irritability	Memory impairment	Spasticity
			Labile emotions		Dysarthria
			Mood swings		
Jordan *et al.* [52] (1997)	Boxers (n = 19)	Disinhibited speech	Depression	Impaired attention	Ataxia
		Disinhibited behavior	Irritability	Altered concentration	Clonus
			Flat affect	Memory impairment	Dysarthria
			Mania		Spasticity
					Tremor
					Unsteady gait
Omalu *et al.* [29,53,54] (2005, 2006, 2010)	Football and wrestling (n = 5)	Paranoid delusions	Suicidality	General cognitive impairment	-
		Social isolation	Anxiety	Memory impairment	
		Physical violence	Labile emotions	Language difficulties	
	Confirmed CTE (5)		Irritability	Executive dysfunction	

Table 1 Summary of published cases describing the clinical features of chronic traumatic encephalopathy *(Continued)*

			Insomnia	Impaired attention	
			Depression		
Mckee *et al.* [2] (2013)	Boxing, American football, ice hockey, wrestling (n = 64)	Explosivity	Depression	Memory impairment	Dysarthria
		Aggression	Hopelessness	Executive dysfunction	Gait disturbance
		Impulsivity	Suicidality	Impaired attention	Parkinsonism
		Paranoia	Mood swings	Language difficulties	
				Visuospatial difficulties	
	Confirmed CTE (64)			Dementia	

CTE, chronic traumatic encephalopathy.

were ice hockey players, and two were professional wrestlers. The clinical features described in all of the cases were classified into one of four categories: behavioral, mood, cognitive, and motor. Table 2 summarizes the clinical features most commonly described across all cases. In 68% of cases, the course of the clinical syndrome was described as progressive. In cases in which a distinction in clinical syndrome was made, the behavioral and mood features were reported to be more stable, whereas the cognitive features were described as progressive, often resulting in dementia. Compared with cases described as progressive, cases described as stable were substantially younger. A large number of cases had a period of latency of several years between the end of exposure to head impacts and the presentation of clinical signs and symptoms. In neuropathologically confirmed cases, authors described the initial clinical presentation as involving mood or behavioral disturbance (or both) without cognitive impairment in 28%, as having cognitive impairment without concurrent mood or behavioral difficulties in 32%, and as having initial mixed cognitive and mood/behavioral disturbance in 40%.

In recent years, some authors have made the distinction between 'classic CTE' and 'modern CTE' [34,36]. For example, McCrory and colleagues [36] define the classic CTE syndrome based on the clinical descriptions from Roberts [49] and the neuropathological reports from Corsellis and colleagues [50]. Based on these earlier cases of boxers, classic CTE is described as having prominent motor features, including gait disturbance, dysarthria, and pyramidal problems, but without progressive cognitive, behavioral, or mood changes [36]. However, it is important to note that, in his monograph, Roberts [49] clarifies that he is intentionally focusing on the description and quantification of motor signs related to

Table 2 Summary of clinical features of chronic traumatic encephalopathy found in the literature

Behavioral features	Mood features	Cognitive features	Motor features
Explosivity	Depression	Dementia	Ataxia
Loss of control	Hopelessness	Memory impairment	Dysarthria
Short fuse	Suicidality	Executive dysfunction	Parkinsonism
Impulsivity	Anxiety	Lack of insight	Gait Disturbance
Aggression	Fearfulness	Perseveration	Tremor
Rage	Irritability	Impaired attention and	Masked facies
Physical violence	Labile emotions	concentration	Rigidity
Verbal violence	Apathy	Language difficulties	Muscle weakness
Inappropriate speech	Loss of interest	Dysgraphia	Spasticity
Boastfulness	Fatigue	Alogia	Clonus
Childish behavior	Flat affect	Visuospatial	
Social inappropriateness	Insomnia	difficulties	
Disinhibited speech	Mania	General cognitive impairment	
Disinhibited behavior	Euphoria	Reduced intelligence	
Paranoid delusions	Mood swings		
Personality changes	Prolix		
Psychosis			
Social isolation			

neurological lesions, reducing his focus on 'the evidence of dementia or personality change' which he viewed as occurring in a subset of cases [49]. In contrast, 'modern CTE' [34,36], defined as any case report published in 2005 or later, is characterized by predominant mood and behavioral symptoms as well as later progressive cognitive deficits and dementia but with less prevalent motor features. We view this distinction between the earlier and more recent descriptions of the clinical presentation of CTE as largely an artifact of different sources of trauma exposure (that is, predominantly boxers in the 'classic' cases and predominantly football players in the 'modern' cases).

To explore this issue, we examined further the cases of neuropathologically confirmed pure CTE described in the series of McKee and colleagues [2] and compared the presence of motor features reported for the deceased professional boxers with those reported for the professional football players. The percentage of professional boxers with motor features (71%) far exceeded that of professional football players (13%). Additionally, it was found that in cases with the most advanced stage of CTE neuropathology, there was a striking difference in the presence of cerebellar pathology in professional boxers (83%) and professional football players (57%). The likely cause of this may be related to the differences in the biomechanics of the head trauma that is experienced through the practice of these two different sports [14].

Previously published diagnostic criteria

To date, there have been two published sets of diagnostic criteria for the clinical diagnosis of CTE. The first diagnostic criteria, proposed by Jordan [35,40,41], were developed specifically to represent the likelihood of underlying CTE neuropathology. As such, the following four diagnostic classifications are used: (1) definite CTE ('any neurological process consistent with the clinical presentation of CTE along with pathological confirmation'), (2) probable CTE ('any neurological process characterized by two or more of the following conditions: cognitive and/or behavioral impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process and consistent with the clinical description of CTE'), (3) possible CTE ('any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders'), and (4) improbable CTE ('any neurological process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiological process unrelated to brain trauma') [35].

In contrast to Jordan's diagnostic criteria, which are focused on the prediction of underlying CTE neuropathology, the diagnostic criteria of Victoroff [27] are focused on a broad set of clinical signs and symptoms representing a diverse set of possible etiologies and are not meant to predict underlying CTE neuropathology. These provisional research diagnostic criteria for clinically probable traumatic encephalopathy (TE) and clinically possible TE were based on the frequency of clinical symptoms and signs reported in TE case reports published between 1928 and 2010. The Victoroff criteria represent an important addition to the literature but have several limitations. For example, for a diagnosis of clinically probable TE, there is a requirement for two symptoms and three signs. However, there is tremendous overlap and redundancy between the symptoms and the 'neurobehavioral signs', including the use of the following terms included as both symptoms and signs: memory loss, irritability, apathy, impulsivity, depression, lability, euphoria, paranoia, and others. Another required criterion for clinically probable TE is the 'persistence of both symptoms and signs for at least two years after the traumatic exposure' [27]. This is not consistent with numerous cases of neuropathologically confirmed CTE for which a delayed onset of the clinical presentation is often observed, representing the neurodegenerative nature of the disease [2,14]. An additional limitation to the Victoroff criteria is the lack of any subtyping of the clinical presentation. That is, the same diagnosis of clinically probable TE could be given to an 80-year-old with memory loss, mental slowing, headache, and nystagmus and to a 22-year-old with depression, anxiety, irritability, and anger. This lack of diagnostic subtyping for a condition with such clinically diverse signs and symptoms would reduce the utility of the criteria for research aimed at elucidating specific clinico-pathological relationships or clinical trials requiring greater specificity of diagnosis to ensure meaningful target outcomes. The criteria are presented in a single table without accompanying descriptive prose, making implementation of the criteria potentially subject to individual interpretation. Finally, the Victoroff criteria do not include or recommend the future use of objective diagnostic tests, such as neuroimaging or other potential biomarkers, to improve upon the diagnostic accuracy, specificity, or ability to detect CTE during life.

Proposed research diagnostic criteria for traumatic encephalopathy syndrome

We propose research diagnostic criteria that address many of the limitations of the previously published criteria by Jordan [35,40,41] and Victoroff [27]. These new criteria are derived from the previous literature on CTE reviewed above as well as the specific findings from the studies by Stern and colleagues [14] and McKee and colleagues [2] on the clinical presentation of neuropathologically confirmed cases of CTE. The term 'traumatic encephalopathy syndrome' (TES) was selected instead of 'chronic traumatic encephalopathy' (CTE) for the following reasons:

(1) we view the designation 'CTE' as a neuropathologically defined disease (which is defined by the characteristic deposition of p-tau pathology) rather than a clinical syndrome; (2) TES is meant to describe the clinical presentation of CTE as well as other possible long-term consequences of repetitive head impacts (for example, chronic or progressive axonopathy without tauopathy) but is not meant to include the acute or post-acute manifestations of a single concussion, post-concussion syndrome, or moderate to severe TBI; (3) the use of the word 'chronic' in CTE inaccurately connotes a stable condition rather than a progressive disorder [27]; and (4) the inclusion of the term 'syndrome' appropriately describes the cluster of clinical features that make up this condition. The proposed research diagnostic criteria for TES include five general criteria, three core clinical features, and nine supportive features that are used to define subtypes of TES: a behavioral/mood variant, a cognitive variant, a mixed variant, and TES dementia. The modifiers 'progressive course', 'stable course', and 'unknown/inconsistent course' are used to describe the clinical course, and if specific motor signs are evident, the modifier 'with motor features' is added.

The selection of the five general criteria was based on the literature reviewed above and was designed to favor sensitivity over specificity. This decision is consistent with the previously published diagnostic criteria [27,35] and is appropriate at this early stage of clinical research into this area. To be included as a core clinical feature, the sign or symptom must have been reported in a minimum of 70% of the cases in the study by Stern and colleagues [14] of neuropathologically confirmed cases of pure CTE. This is in contrast to the algorithm employed in the Victoroff [27] diagnostic criteria for which a sign or symptom was included if it was present in at least 7% of the case reports he reviewed from the literature. The nine supportive features were selected to increase specificity once the general criteria are met and are based on features reported in the previous literature.

The clinical diagnosis of TES is not meant to imply a certainty of underlying CTE neuropathological changes (for example, p-tau accumulation). Rather, TES is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma. It is expected that some individuals with TES do indeed have CTE neuropathological changes. However, it is also possible that some individuals with TES have other underlying causes of their clinical presentation, including, but not limited to, progressive white matter degeneration [55] or AD. For this reason, a separate diagnostic classification for 'possible CTE', 'probable CTE', and 'unlikely CTE' is included, based on the presence of additional supportive features, such as biomarkers, which indicate the degree to which the underlying etiology of the clinical presentation of TES is likely due to the CTE pathophysiological process. Finally, we offer six cases (see boxes) as exemplars of the implementation of the TES criteria; each case is a composite of several patients and is created specifically for this purpose.

At this time, risk factors for CTE (above and beyond brain trauma) remain unknown. Among possible variables under investigation by our group and other laboratories are the quantity or severity (or both) of the brain trauma, the initial age and overall duration of head impact exposure, lifestyle factors, and genetic susceptibility. Based on current research findings, it is expected that TES is the clinical manifestation of underlying damage or dysfunction of cortical or subcortical brain structures (or both) and is associated with a history of repetitive brain trauma, including both symptomatic concussions and subconcussive trauma. Although some investigators have suggested that a single moderate to severe TBI may lead to CTE [37] or AD [56] or both, the use of the clinical diagnosis of TES at this time is meant to be used for individuals with repetitive impacts to the head, as defined below. We have included a requirement for a specific minimal amount of exposure to head impacts. This is based on previous findings of post-mortem confirmed CTE cases [1,2,5,50] and will be subject to revisions as additional research is conducted on exposure variables.

General criteria for traumatic encephalopathy syndrome

All five criteria must be met for a diagnosis of TES:

1. History of multiple impacts to the head (or to the body resulting in impulsive force transmitted to the head). Multiple impacts are defined based upon (a) the types of injuries and (b) the source of exposure.
   a. Types of injuries:
      i) Mild TBI or concussion, defined according to the Zurich 2012 Consensus Statement on Concussion in Sport [57] as a 'complex pathophysiological process affecting the brain, induced by biomechanical forces...caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force transmitted to the head...the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness'. History of this form of trauma can be based on documented records from health-care providers or on self- or informant-reports, after being given an appropriate definition of 'concussion' [58]. If there is no reported exposure to other

repetitive hits to the head, there should be a minimum of four documented mild TBIs or concussions.

ii) Moderate/severe TBI, defined as having loss of consciousness of at least 30 minutes, alteration of consciousness/mental state of more than 24 hours, post-traumatic amnesia of more than 24 hours, and Glasgow Coma Scale score of less than 13 [59]. If there is no reported exposure to other repetitive hits to the head, there should be a minimum of two moderate/severe TBIs.

iii) 'Subconcussive' trauma, defined as biomechanical force to the head or body similar to, or less than, that required for symptomatic concussion but without symptoms and clinical presentation consistent with concussion [3,4].

b) Source of exposures:

i. Involvement in 'high exposure' contact sports (including, but not limited to, boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer) for a minimum of 6 years, including at least 2 years at the college level (or equivalent) or higher.

ii. Military service (including, but not limited to, combat exposure to blast and other explosions as well as non-combat exposure to explosives or to combatant or breach training).

iii. History of any other significant exposure to repetitive hits to the head (including, but not limited to, domestic abuse, head banging, and vocational activities such as door breaching by police).

iv. For moderate/severe TBI, any activity resulting in the injury (for example, motor vehicle accident).

2) No other neurological disorder (including chronic residual symptoms from a single TBI or persistent post-concussion syndrome) that likely accounts for all clinical features, although concomitant diagnoses of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (for example, AD and frontotemporal dementia) or a combination of these can be present.

3) Clinical features must be present for a minimum of 12 months. However, if treatment (for example, 'antidepressant' medication) results in an improvement in select symptoms, the clinician should use her or his best judgment to decide whether the symptoms would have persisted or progressed if treatment had not been initiated.

4) At least one of the core clinical features must be present and should be considered a change from baseline functioning.

5) At least two supportive features must be present.

Core clinical features of traumatic encephalopathy syndrome

At least one of the core clinical features must be present:

1) *Cognitive.* Difficulties in cognition:
   a) as reported by self or informant, by history of treatment, or by clinician's report of decline; and
   b) substantiated by impairment on standardized mental status or neuropsychological tests of episodic memory, executive function, and/or attention, as defined by scores at a level of at least 1.5 standard deviations below appropriate norms.
2) *Behavioral.* Being described as emotionally explosive (for example, having a 'short fuse' or being 'out of control'), physically violent, and/or verbally violent, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of intermittent explosive disorder would meet this criterion but is not necessary.
3) *Mood.* Feeling overly sad, depressed, and/or hopeless, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary.

Supportive features of traumatic encephalopathy syndrome

A minimum of two of the following features must be present for a diagnosis of TES:

1) *Impulsivity.* Impaired impulse control, as demonstrated by new behaviors, such as excessive gambling, increased or unusual sexual activity, substance abuse, excessive shopping or unusual purchases, or similar activities.
2) *Anxiety.* History of anxious mood, agitation, excessive fears, or obsessive or compulsive behavior (or both), as reported by self or informant, history of treatment, or clinician's report. A formal diagnosis of anxiety disorder would meet this criterion but is not necessary.
3) *Apathy.* Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors, as reported by self or informant, history of treatment, or clinician's report.
4) *Paranoia.* Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy.
5) *Suicidality.* History of suicidal thoughts or attempts, as reported by self or informant, history of treatment, or clinician's report.
6) *Headache.* Significant and chronic headache with at least one episode per month for a minimum of 6 months.
7) *Motor signs.* Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other

features of parkinsonism. If present, the modifier 'with motor features' should be used (see below).

8) *Documented decline.* Progressive decline in function and/or a progression in symptoms and/or signs, based upon repeated formal testing, clinician examination, or other formal measurement (for example, informant questionnaire) for a minimum of 1 year.
9) *Delayed onset.* Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure. It should be noted, however, that individual cases may begin to develop the clinical features of TES during their period of head impact exposure (for example, while still actively involved in a collision sport), especially older individuals or those who have been engaged in the high-exposure activity for many years. It may also be difficult to differentiate the clinical presentation of prolonged or persistent post-concussion syndrome (pPCS) from that of TES. Therefore, there could be cases for whom there is overlap of resolving pPCS and the initial features of TES, thus masking any delayed onset of TES.

Traumatic encephalopathy syndrome diagnostic subtypes}

1) TES behavioral/mood variant (TES-BMv)
   a) Behavioral or mood core features (or both) without cognitive core features.
2) TES cognitive variant (TES-COGv)
   a) Cognitive core features without behavioral or mood core features (or both).
3) TES mixed variant (TES-MIXv)
   a) Both cognitive core features and behavioral or mood core features (or both).
4) TES dementia (TES-D)
   a) Progressive course of cognitive core features with or without behavioral or mood core features (or both).
   b) Evidence of 'functional impairment', defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living. The determination of functional impairment is based on clinician's judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges.
   c) If the clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease (for example, frontotemporal dementia), both diagnoses may be given, either with one being 'primary' and the other being 'secondary' or with the term 'mixed' used if neither is presumed primary.

'With motor features' modifier

For each TES subtype, the modifier 'with motor features' should be added if the individual demonstrates dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism.

Clinical course

For each TES subtype, one of the following additional modifiers should be selected: 'stable course', to be used when the history or objective testing (or both) indicates that there has been little if any change in symptoms, signs, or other measures; 'progressive course', to be used when there is a clear indication of progressive worsening of clinical features for at least a 2-year period; and 'unknown/inconsistent course', to be used when either there is too little information available about the clinical course or the course has been inconsistent, with periods of stability, worsening, and/or improvement. By definition, TES dementia has a progressive course and does not require this modifier.

'Possible CTE' and 'probable CTE'

As stated above, CTE is a neuropathological diagnosis, whereas TES is a clinical diagnosis. As with other neurodegenerative diseases, such as AD, it is not possible at this time to diagnose the underlying disease with certainty during life. However, again as with other neurodegenerative diseases and in keeping with the diagnostic criteria for CTE proposed by Jordan [35,40,41], we propose provisional diagnostic classifications of 'probable CTE', 'possible CTE', and 'unlikely CTE'. Because the scientific study of the clinical presentation of CTE is only in its infancy, it is not yet possible to create meaningful diagnostic criteria for 'probable CTE' based solely on clinical features and course, such as those employed for the National Institute on Aging-Alzheimer's Association (NIA-AA) AD diagnostic criteria for probable AD dementia [60], a condition that has been carefully studied for many decades. Rather, we propose, as a starting point, several potential *in vivo* biomarkers for CTE that can be used to support a provisional diagnosis of 'probable CTE'. This diagnosis would be analogous to the NIA-AA diagnosis of probable AD dementia with evidence of the AD pathophysiological process [60]. However, because of the early stage of research into potential CTE biomarkers, we refrain from using this type of nomenclature. The following list of potential biomarkers for underlying CTE is meant only as a guideline at this early point in CTE diagnostic research. Many of these biomarkers are the focus of current research but have not yet been

formally validated. Future biomarker validation studies will likely add to or delete (or both) items on this list. Moreover, we do not in any way recommend that the specific tests used for these potential biomarkers be conducted for clinical purposes at this time.

Potential biomarkers for the diagnosis of probable chronic traumatic encephalopathy

1) *Cavum septum pellucidum*. Report of cavum septum pellucidum, cavum vergae, or fenestrations based on neuroimaging study.
2) *Normal beta amyloid cerebrospinal fluid (CSF) levels*. CSF beta amyloid levels in the normal range for age and not diminished as would be suggestive of AD.
3) *Elevated CSF p-tau/tau ratio*. CSF p-tau/total tau ratio above the normal range for age.
4) *Negative amyloid imaging*. PET amyloid imaging (for example, florbetapir and flutemetamol) in the normal range, not suggestive of AD.
5) *Positive tau imaging*. PET paired helical filament tau imaging suggestive of abnormal tau deposition. It should be noted that this remains an experimental procedure and requires additional validation prior to its use as a research tool for diagnostic purposes.
6) *Cortical thinning*. Based on magnetic resonance imaging (MRI) measurement, evidence of abnormal cortical thinning indicative of neurodegeneration.
7) *Cortical atrophy*. Based on MRI or computed tomography, generalized cortical atrophy beyond what is expected for age, and, in particular, frontal, thalamic, hippocampal, and/or amygdalar atrophy.

Chronic traumatic encephalopathy classification

1) Probable CTE. Meets classification for any TES subtype, progressive course; does not meet diagnostic criteria for another disorder more consistently than TES; and has a minimum of one positive potential biomarker for CTE.
2) Possible CTE. Meets classification for any TES subtype, progressive course, and (1) has not undergone any potential biomarker testing, (2) has had negative results on one or more biomarkers with the exception of PET tau imaging (that is, if a negative PET tau imaging finding, the current classification would be 'unlikely CTE'), or (3) meets the diagnostic criteria for another disorder that, on its own, could account for the clinical presentation.
3) Unlikely CTE. Does not meet TES diagnostic criteria or has had a negative PET tau imaging scan or both.

Case A A 45-year-old married man with a history of playing multiple contact sports, including soccer (ages 5 to 13), hockey (ages 7 to 12), and football (ages 9 to 22) presented to his primary care physician. He played college football at a Division 1 university and was an offensive lineman. He had no reported or formally diagnosed concussions, although when provided with a definition of concussion, he stated that he likely had 20 to 30 throughout high school and college. Since graduating from college, he has worked as an auditor for state government. His work performance evaluations had been routinely positive, although for the past two years they have been marred by reports of 'careless errors', reduced productivity, and one episode of yelling at his immediate supervisor. His wife of 16 years reports that he has had a 5- to 7-year history of worsening behavior, with frequent episodes of having a 'short fuse' and losing his temper with their two young children. Though always a social drinker, he has had frequent episodes of binge drinking over the past 2 to 3 years. She states that his personality has changed from a kind, even-keeled, loving man to an argumentative, explosive, and moody individual. Both he and his wife state that he was high-functioning, without any cognitive, mood, and behavioral problems during the time period between college and about age 35. He recently underwent formal neuropsychological evaluation that demonstrated moderately impaired sustained attention, mildly impaired delayed recall on a word list, and moderately impaired executive functioning as measured by a card-sorting test. All other areas of functioning were within the normal range. A self-report measure of syndromal depression indicated mild to moderate severity. Other than the recent work-performance evaluations, there were no other reports of significant functional decline. The result of a recent brain MRI was unremarkable other than some mild, scattered white matter abnormalities. Other medical history, laboratory findings, and neurological examination were unremarkable. Diagnosis: TES-MIXv, progressive course; possible CTE.

Case B A 31-year-old single female Army veteran was referred to the VA Medical Center Behavioral Health Clinic for a 14-month history of suicidal thoughts, agitation, and aggressive behavior. She had reached the rank of staff sergeant and was a logistics specialist. She was honorably discharged 1 year ago, began working in her family's grocery store, but had to stop

working 6 months ago because of her neuropsychiatric symptoms. She had two deployments to Afghanistan and denied being directly involved in combat. However, she reported that 20 months prior to her discharge, she was thrown off a truck when it struck an improvised explosive device. She was told she landed on her head and lost consciousness for 2 to 3 minutes. Upon regaining consciousness, she reported 'seeing stars' and had a headache that lasted 3 to 4 days. She denied these symptoms to the medic when questioned and remained on active duty. About 3 months later, a heavy box fell on her head, throwing her to the floor. She denied loss of consciousness but was nauseated and had balance difficulties for several hours. She complained of being in a fog and irritable for 2 days following the accident. Her tour of duty ended 2 weeks later and she returned home. Other than those two injuries, she denied any TBIs or concussions. These symptoms completely cleared, and she described her functioning, including her mood, as 'completely fine' between that time and about 14 months ago. Prior to enlisting, she was an avid ice hockey player, having played since the age of 5, and was the captain of her high school team. Her medical and psychiatric histories were unremarkable, and laboratory results of tests ordered by her primary care physician were normal. At the current evaluation, a mental status examination was conducted and the results were generally within normal limits. She denied having any cognitive complaints. A psychiatric interview revealed significant overall distress, with suicidal ideation without any active plan. Her primary complaints included poor sleep, sadness, anxiety, agitation, and being overly aroused by loud noises. She denied having any flashbacks or night terrors. A sibling was interviewed and corroborated the description and history but added that for the past year she had been verbally aggressive and explosive, frequently yelling at family members for no apparent reason, and that these episodes seemed to turn off and on without any warning. The sibling stated that these abnormal behaviors have been somewhat consistent over the past year. A PTSD specialist examined the patient, reported that she would not meet criteria for PTSD, and questioned whether the symptoms were residual from her TBIs in Afghanistan. The result of a brain MRI was unremarkable. Diagnosis: TES-BMv, stable course; possible CTE.

Case C A 59-year-old man presented to his primary care physician with complaints of progressive memory and concentration problems. Prior to going to college, the patient entered the Army, where he boxed competitively for 4 years. He did not experience any combat. He was an avid rugby player in college and continued playing in formal competitive clubs until the age of 54, when he stopped because of a cervical disk injury. He received an MBA and had been a successful business consultant. He was divorced at the age of 45 and lived alone. He reported one concussion at the age of 30, when he briefly lost consciousness during a rugby game, although he stated he got his 'bell rung' countless times in boxing and rugby. He reported to his primary care physician that he had been having difficulty remembering details of conversations and meetings at work and that this was beginning to interfere with his productivity. His medical history was significant for the cervical disk injury and for migraine headaches for many years. He was referred to a local academic medical center memory clinic, where a formal neuropsychological evaluation demonstrated moderately impaired performance on a word list recall task, compared with age and education norms, as well as severely impaired fine motor dexterity. All other areas were intact, although his performance on a measure of psychomotor speed and response set maintenance was slightly below expected levels given his history. A neurological examination revealed mild bilateral resting tremor and mild upper extremity rigidity. An MRI scan was read as normal, and all laboratory findings were within normal limits. As part of a clinical research study, he was given two PETs: one with a new tau radiotracer and another with an amyloid tracer. Results indicated no meaningful amyloid uptake, although his tau scan was abnormal with scattered increased tracer uptake in the dorsolateral frontal cortex and the medial temporal lobes. Diagnosis: TES-COGv, with motor features, progressive course; probable CTE.

Case D A 69-year-old former National Football League (NFL) football player was seen in consultation following a 10-year progressive decline. He had seen several physicians and

had been given multiple diagnoses, including frontotemporal dementia and dementia due to AD. He had played professional football for 9 years as a linebacker. He began playing football in high school and played for a Division 1 college for 4 years, playing both as a linebacker and as an offensive lineman. Following retirement from the NFL, he had a successful career in commercial real estate until he was forced to retire at the age of 62 because of 'poor decision-making and judgment'. His wife of 25 years stated that, in retrospect, he was demonstrating poor memory and judgment for about 3 years prior to his retirement and that these problems had progressively worsened through the years. She stated that he also began having significant difficulties with multi-tasking and 'numbers' at age 61 and was having difficulty with household finances and hobbies. After retirement, he became increasingly withdrawn and refused to socialize. In contrast to his previous jovial and easy-going manner, he became verbally aggressive toward his wife and children, 'blowing up over small things'. On two occasions, he became physically aggressive toward his wife, requiring her to call the police. He never demonstrated any disinhibited or socially inappropriate behavior, nor was there any report of hallucinations or movement disturbance. In the past 2 years, his functioning has worsened; he now has no 'short-term memory', watches television all day long, and has an erratic sleep cycle. He is functionally impaired in all instrumental activities of daily living as well as in some basic activities of daily living. His medical history is significant for a myocardial infarction at age 54, hypertension, severe arthritis, and multiple lumbar disk surgeries. There is no family history of dementia. Upon examination, he was disoriented to time and place, was perseverative, and could not recall recent current events. He exhibited some frontal release signs, although the result of his motor examination was otherwise normal. His Mini-Mental Status Exam score was 9, and his Clinical Dementia Rating was 2.0. A neuropsychological evaluation was conducted and demonstrated severe episodic memory impairment as well as profoundly impaired performance on most tests of executive functioning. In contrast, attentional capacity was within normal limits and language was relatively intact. A brain MRI revealed significant global atrophy with marked hippocampal atrophy as well as a cavum septum pellucidum. An amyloid PET scan demonstrated only minimal uptake, not commensurate with the degree of dementia. Diagnosis: TES-D; probable CTE.

Case E A 31-year-old male stockbroker saw his primary care physician because of an 18-month history of recurrent headaches, irritability, agitation, and a worsening 'short fuse'. He had been taking oxycodone (left over from previous oral surgery) for his headache pain. He was referred to a neurologist, who specialized in headache and who diagnosed him with tension headache. However, when asked if he had ever had headaches previously, the patient reported that he frequently had them as a teenager after his varsity high school football games and when he played rugby for 2 years in college. Because of this history of prior exposure to repetitive head impacts and possible symptomatic concussions, the neurologist referred him to a psychiatrist colleague to evaluate him for possible depression and suicidality, based on the neurologist's belief that the patient might have CTE; he had recently attended a talk on sports injuries. The consulting psychiatrist interviewed the patient, who acknowledged that he had frequent suicidal ideation following the breakup of his marriage about 1 year earlier but that these thoughts had now diminished. Although the patient formally met criteria for TES-BMv, the psychiatrist felt that the headache symptoms, suicidality, short fuse, and irritability were likely associated with the divorce. The patient was prescribed citalopram as well as regular therapeutic massage for his tension headache and was seen in 3 months, at which time he reported substantial improvement of his mood and behavioral symptoms and a complete resolution of his headaches. Diagnosis: adjustment disorder, persistent with mixed anxiety and depressed mood; unlikely CTE.

Case F An 81-year-old widowed man enrolled in a research study examining the long-term consequences of TBI. He reported having sustained a moderate TBI in a motor vehicle accident at the age of 46 with loss of consciousness for approximately 1 hour. He was hospitalized for 3 days because of confusion and memory difficulties that mostly resolved prior to discharge. He was unable to return to work as a high school physical education teacher and coach for several weeks because of continued cognitive difficulties, headache, and

balance problems. He reported that, once he returned to work, he 'didn't feel normal' for several months. He continued working until retirement at age 60. He played high school and college football and reported having had his 'bell rung' 'all the time'. According to his adult son (with whom he lived), he was 72 when he began having memory problems that gradually progressed over the course of 5 to 6 years. In the past few years, the memory problems worsened significantly, such that he could not recall events that occurred more than an hour earlier. In addition, he had worsening problems with judgment, decision-making, multi-tasking, and word-finding. He no longer drove and was dependent in most areas of instrumental activities of daily living. He lacked interest in all activities and appears 'depressed' according to his son. His medical history was significant for prostate cancer, controlled hypertension, arthritis, and glaucoma. Two brothers died in their 80s with 'dementia'. Neuropsychological testing revealed significant impairments in episodic memory, confrontation naming, psychomotor speed, and many aspects of executive functioning. Research-based MRI revealed frontal and temporal atrophy and a pronounced cavum septum pellucidum; diffusion tensor imaging and tractography demonstrated significant reductions in corpus callosum fiber bundles. PET amyloid imaging showed elevated uptake consistent with AD. Diagnosis: dementia due to AD pathophysiological process and TES-D, mixed; possible CTE.

The current proposed research diagnostic criteria for TES are meant to be a starting point that should be modified and updated as new research findings in the field become available and as future research using these criteria are published. These proposed criteria are not meant to be used for a clinical diagnosis or as evidence of an underlying disease. Rather, they should be viewed as research criteria that could be employed in studies of the underlying causes, risk factors, differential diagnosis, prevention, and treatment of TES. Future studies comparing these proposed diagnostic categories with post-mortem neuropathological diagnoses, as well as with appropriate *in vivo* biomarkers for CTE and other conditions, will help lead to the transition from 'research' criteria to 'clinical' criteria. It also would be critical for these proposed criteria to undergo a formal expert consensus approval process, such as that used for the NIA-AA Diagnostic Guidelines for Alzheimer's Disease [60].

One important factor that must be addressed in future iterations of these criteria is that of base rates. That is, the population prevalence of most of the core clinical features and many of the supplemental features of TES presented below is relatively high. Therefore, it is possible to meet criteria for TES and yet have an idiopathic disorder or a situationally based condition that is unrelated to the earlier history of head impact exposure. The inclusion of supportive features is meant to reduce this lack of specificity to a degree, but, at this time, we acknowledge that these criteria will likely result in very high sensitivity at the expense of specificity. With the utilization of future research findings and subsequent criteria revisions, it is likely that the specificity will increase. An important additional issue regarding the use of these criteria involves the impact of litigation or disability determination (or both) on the validity of symptom reporting and neuropsychological test performance. It is therefore recommended that this issue be taken into account when interpreting the individual's self-reported functioning and test performance and that formal symptom validity checking be conducted as part of any formal evaluation. Until future research yields accurate biomarkers and allows clarification and modification of the proposed criteria, the decision as to whether an individual meets the TES diagnostic criteria and associated 'probable CTE' diagnostic criteria should be left up to the individual researcher, clinician, or, preferably, a multidisciplinary diagnostic adjudication process.

Conclusions

The long-term consequences of repetitive head impacts have been known since the beginning of the 20th century. Although the clinical presentation of CTE is varied and non-specific, there are adequate reports to date to suggest that there may be two clinical subtypes: one subtype involving primarily behavioral or mood features (including explosivity or violence) or both, and the other involving cognitive deficits (including impairments in episodic memory, executive functioning, and attention). Many individuals progress to dementia, with impaired functional independence, and some individuals develop motor impairments (including parkinsonism, ataxia, and dysarthria). We propose research diagnostic criteria for TES that we hope will facilitate research into this area. There are expected limitations to the development of diagnostic criteria based primarily on a relatively small number of case reports. The goal of proposing these criteria at this time is to facilitate research in this nascent area of study. It is expected that these criteria will undergo modification and revision as new research findings become available, additional biomarkers are validated, and future research using these criteria are published.

Note: This article is part of a series on *Traumatic brain injury*, edited by Robert Stern. Other articles in this series can be found at http://alzres.com/series/traumaticbraininjury

Abbreviations

AD: Alzheimer's disease; CSF: Cerebrospinal fluid; CTE: Chronic traumatic encephalopathy; MRI: Magnetic resonance imaging; NFL: National Football League; NIA-AA: National Institute on Aging-Alzheimer's Association; PET: Positron emission tomography; pPCS: Persistent post-concussion syndrome; p-tau: Phosphorylated tau; PTSD: Post-traumatic stress disorder; TBI: Traumatic brain injury; TE: Traumatic encephalopathy; TES: Traumatic encephalopathy syndrome; TES-BMv: Traumatic encephalopathy syndrome behavioral/mood variant; TES-COGv: Traumatic encephalopathy syndrome cognitive variant; TES-D: traumatic encephalopathy syndrome dementia; TES-MIXv: Traumatic encephalopathy syndrome mixed variant.

Competing interests

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EXHIBIT 11

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma

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KEYWORDS

- Encephalopathy, Post-traumatic
- Neurodegenerative disorders • Concussion • Athletic injuries
- Dementia • Motor neuron disease

It has been understood for decades that certain sporting activities may increase an athlete's risk of developing a neurodegenerative disease later in life. Not surprisingly, this association was originally noted in boxers, athletes who receive numerous blows to the head during training and competition. In 1928, Harrison Martland, a New Jersey pathologist and medical examiner, first described the clinical spectrum of abnormalities found in "nearly one half of the fighters who have stayed in the game long enough."[1]

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Boxers exhibiting cognitive, behavioral, or motor abnormalities were well known to lay persons, sportswriters, and others within the boxing community and were referred to by various terms, such as "punch drunk," "goofy," and "slug-nutty"[2,3]; later, the more formal term *dementia pugilistica* was introduced to lend medical validity to the condition.[4] By the 1970s, a sufficient number of boxers with dementia pugilistica had been studied pathologically to support the conclusion that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease.[5] As evidence of the clinical and neuropathologic consequences of repeated mild head trauma grew, it became clear that this pattern of neurodegeneration was not restricted to boxers, and the term chronic traumatic encephalopathy (CTE), originally coined by Miller[6] became most widely used.

Over the last several decades, clinical and neuropathologic evidence of CTE has emerged in association with various sports, including American football, professional wrestling, professional hockey, and soccer, as well as other activities associated with repetitive mild head trauma, such as physical abuse, epileptic seizures, and head banging.[7–13] Although the incidence and prevalence of CTE is currently unclear, it probably varies by sport, position, duration of exposure, and age at the time of initial or subsequent head trauma, and with additional variables, such as genetic predisposition. To date, there have been no randomized neuropathologic studies of CTE in deceased athletes, and as such, there is a selection bias in the cases that have come to autopsy. If one considers the prevalence in deceased professional American football players who died between February 2008 and June 2010, there were 321 known player deaths[14] and the brains of 12 of the 321 underwent postmortem neuropathologic examination at Boston University Center for the Study of Traumatic Encephalopathy (BU CSTE). All 12 examined neuropathologically showed evidence of CTE, suggesting an estimated lifetime prevalence of at least 3.7%. If one assumes that all deceased players who did not come to autopsy did not have CTE and that the amount of head trauma in professional football has remained fairly constant over the past 5 decades, a prevalence of 3.7% would result. Although this represents a conservative estimate, it suggests a significant public-health risk for persons who suffer repetitive mild traumatic brain injury (TBI).

CLINICAL SIGNS AND SYMPTOMS OF CTE

Whereas concussion and postconcussion syndrome represent temporary states of neuronal and axonal derangement, CTE is a neurodegenerative disease that occurs years or decades after recovery from the acute or postacute effects of head trauma. The exact relationship between concussion and CTE is not entirely clear, although repetitive axonal perturbation may initiate a series of metabolic, ionic, membrane, and cytoskeletal disturbances, which trigger the pathologic cascade that leads to CTE in susceptible individuals.[15,16] The onset of CTE is often in midlife, usually after athletes have retired from their sport. In some individuals, the early manifestations of CTE affect behavior; in particular, individuals with neuropathologically documented CTE have been described by family and friends as being more irritable, angry, or apathetic or as having a shorter fuse. Increased suicidality seems to be a particularly salient symptom of CTE.[17] In other cases, cognitive difficulties may be the first signs to emerge, with poor episodic memory and executive functioning being two of the most common cognitive dysfunctions reported. Later in the disease, movement (eg, parkinsonism), speech, and ocular abnormalities may emerge in the context of declining cognition and worsening comportment. A minority of cases with neuropathologically documented CTE developed dementia before death; the relative infrequency of

dementia in individuals with CTE may be due in part to many individuals with CTE having committed suicide or died from accidents or drug overdose at an early age.[11,17]

NEUROPATHOLOGY OF CTE

Gross Pathology

Neuropathologic studies of athletes with a history of repeated mild head injuries have produced several consistent findings that, together, make CTE a distinctive disorder. On gross examination, there is often anterior cavum septi pellucidi and, usually, posterior fenestrations. These changes may be caused by the force of the head impact being transmitted through the ventricular system, thereby affecting the integrity of the intervening tissue. Enlargement of the lateral and third ventricles is also commonly seen in CTE; the third ventricle may be disproportionately widened. Additional gross features include atrophy of the frontal and temporal cortices and of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Atrophy of the cerebrum, diencephalon, basal ganglia, brainstem, and cerebellum may result in an overall reduction in brain mass.[11]

Microscopic Neuropathology

Tau

Microscopically, CTE is characterized by an abundance of neurofibrillary inclusions in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), and glial tangles (GTs). The main protein composing NFTs is the microtubule-associated protein tau, and NFTs are aggregates of filamentous tau polymers. Although CTE shares many microscopic similarities with Alzheimer disease (AD) and other tauopathies, it has several distinguishing features. First, the distribution of tau pathology is unique; it is most commonly found in the more superficial cortical laminae (II and III), whereas tau NFTs in AD are preferentially distributed in large projection neurons in layers III and V. Further, the regional tau pathology is extremely irregular, largely confined to uneven foci in the frontal, temporal, and insular cortices, unlike the more uniform cortical NFT distribution seen in AD. Tau NFTs, NTs, and GTs are found throughout the medial temporal lobe, often in densities greater than those found in severe AD, and are also prominent in the diencephalon, basal ganglia, and brainstem. NTs and GTs are also found in the subcortical white matter. Finally, NFTs in CTE are most dense at the depths of cortical sulci, and are typically perivascular, which might indicate that disruptions of the cerebral microvasculature and the blood brain barrier that occur at the time of the traumatic injury play a critical role in the formation of NFTs.[11]

Although the precise pathologic mechanisms that tie repeated mild head injuries to NFT formation are not known, they may involve a series of diffuse axonal injuries (DAI) set in motion by the initial trauma and aggravated by subsequent mild traumatic injuries. During a TBI, the brain and spinal cord undergo shear deformation producing a transient elongation or stretch of axons. Traumatic axonal injury results in alterations in axonal membrane permeability, ionic shifts including massive influx of calcium, and release of caspases and calpains that might trigger tau phosphorylation, misfolding, truncation, and aggregation, as well as breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments.[15,18,19]

Increasing evidence indicates that tau phosphorylation, truncation, aggregation, and polymerization into filaments represents a toxic gain of function, and continued accumulation of tau leads to neurodegeneration. This is supported by tau's involvement in some genetic forms of frontotemporal degeneration[20] and by work that shows

that plasmids containing human tau complementary DNA constructs microinjected into lamprey neurons in situ produce tau filaments that accumulate and lead to neuronal degeneration.[21,22] However, it is also possible that the intracellular NFTs, by themselves, are the byproducts rather than the cause of cellular injury and that NFT formation indicates neurons that survived the initial injury and sequestered the abnormally phosphorylated, truncated, and folded tau.[23] A possible tau toxic factor or transcellular propagation by the misfolded tau protein may explain how a neurodegeneration that starts multifocally around small blood vessels or in the depths of cortical sulci ultimately spreads to involve large regions of brain as a systemic degeneration, such as CTE.[24]

Beta-amyloid

Beta-amyloid (Aβ) deposits are found in 40% to 45% of individuals with CTE, in contrast to the extensive Aβ deposits that characterize nearly all cases of AD. Although neuritic plaques are typically abundant in AD and are essential to the diagnosis, Aβ plaques in CTE, when they occur, are less dense and predominantly diffuse.[11] Despite the fairly minor role Aβ plaques seem to play in the neuropathologic manifestation of CTE, the role of Aβ in the pathogenesis of CTE has yet to be elucidated. It is known that acute head injuries cause an upregulation of amyloid precursor protein (APP) production and that Aβ plaques may be found in up to 30% of patients who die within hours of TBI.[25–27] DAI, often a consequence of mild TBI, is thought to influence changes in Aβ after head injury. Interruption of axonal transport causes an accumulation of multiple proteins in the axon, including APP, in varicosities along the length of the axon or at disconnected axon terminals, termed axonal bulbs.[28] Although the axonal pathology in TBI is diffuse in that it affects widespread regions of the brain, typically, the axonal swellings are found in multifocal regions of the subcortical and deep white matter, including the brainstem. Because of the rapid and abundant accumulation of APP in damaged axons after TBI, APP immunostaining is used for the pathologic assessment of DAI in humans. Accordingly, this large reservoir of APP in injured axons might be aberrantly cleaved to rapidly form Aβ after TBI.[25,29,30] However, it remains unclear whether the large quantities of APP and Aβ found in damaged axons after TBI play any mechanistic role in neurodegeneration or neuroprotection.[28,31,32] Moreover, it is unknown how long the increased APP and Aβ lasts or what mechanisms may result in variable clearance.

TDP-43

Recently, in addition to severe tau neurofibrillary pathology, the authors found a widespread TDP-43 proteinopathy in more than 80% of their cases of CTE.[13] Moreover, in 3 athletes with CTE who developed a progressive motor neuron disease several years before death, there were extensive TDP-43 immunoreactive inclusions in the anterior horns of the spinal cord, along with tau-immunoreactive GTs, neurites, and, occasionally, extensive NFTs. These findings suggest that a distinctive, widespread TDP-43 proteinopathy is also associated with CTE and that, in some individuals, the TDP-43 proteinopathy extends to involve the spinal cord and is clinically manifest as motor neuron disease with a presentation that may appear similar to amyotrophic lateral sclerosis (ALS).[13] The shared presence of 2 aggregated phosphorylated proteins associated with neurodegeneration in the great majority of cases of CTE suggests that a common stimulus, such as repetitive axonal injury, provokes the pathologic accumulation of both proteins.[33] Recent studies in vitro and in vivo suggest that overexpression of wild-type human TDP-43 and its dislocation from the neuronal nucleus to the cytoplasm are associated with neurodegeneration and cell death.[34–36] By virtue

of its capacity to bind to neurofilament messenger RNA (mRNA) and stabilize the mRNA transcript, TDP-43 plays a critical role in mediating the response of the neuronal cytoskeleton to axonal injury. TDP-43 is intrinsically prone to aggregation, and its expression is upregulated after experimental axotomy in spinal motor neurons of the mouse.[37] Traumatic axonal injury may also accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm, thereby enhancing its neurotoxicity.

CLINICAL IMPLICATIONS

CTE is a Potential Late Effect of Repeated Head Injuries

CTE is not thought to be a long-term sequela after a specific head trauma. Rather, its clinical symptoms emerge later in life, usually after athletes retire from their sport. Like most other neurodegenerative diseases that cause dementia, CTE has an insidious onset and gradual course. Based on a recent review of neuropathologically confirmed CTE in athletes[11], the mean age at onset is 42.8 years (SD = 12.7; range = 25–76 years). On average, onset occurs approximately 8 years after retirement (SD = 10.7), although approximately one-third of athletes were reportedly symptomatic at the time of retirement. In athletes, the course seems to be considerably protracted (mean duration = 17.5 years, SD = 12.1), especially in boxers. The average duration of the disease in boxers is 20 years (SD = 11.7) and 6 years in American football players (SD = 2.9).[11] If the affected individual does not die of other causes, full-blown clinical dementia may occur late in the course of the disease.

Diagnosis of CTE

Currently, the clinical diagnosis of CTE is difficult because there are no consensus diagnostic criteria or large-scale longitudinal clinicopathologic correlation studies. The differential diagnosis of CTE often includes AD[38] and frontotemporal dementia (FTD)[39], depending on the age at onset and the presenting problem. Older individuals with memory difficulties may seem to have AD, and, in fact, may have evidence of AD and CTE neuropathologically.[11] When the age at onset is earlier (eg, 40s or 50s) and the patient presents with behavioral dysregulation or apathy, it may be difficult to rule out FTD. Although a history of remote head trauma may be suggestive of CTE, head trauma has been implicated as a risk factor of AD, Parkinson disease, ALS, and other neurodegenerative diseases.[40–42] Therefore, without neuropathologic confirmation, currently, a clinical diagnosis of CTE cannot be made with a high degree of confidence. Furthermore, the clinical phenotype of CTE may be confounded by alcohol or other drug abuse. Several individuals with neuropathologically confirmed CTE are thought to have developed problems with drug abuse as a consequence of the loss of inhibitory control caused by the neurodegenerative disease. From a clinical perspective, however, it can be difficult to determine whether the drug abuse problems are a cause of symptoms or simply one of many ways in which CTE is manifested.

Although the neuropathologic features of CTE seem to be distinct from other neurodegenerative diseases, no currently agreed neuropathologic criteria exist for the diagnosis of CTE. Once established, these criteria can be applied at autopsy in large-scale, prospective longitudinal studies of athletes with a history of repetitive head injuries. Establishing neuropathologic diagnostic criteria would allow for the identification of clinical criteria and biomarkers to improve the accuracy of CTE diagnosis in the living.

Several biomarkers are believed to have the potential to contribute to identifying CTE in vivo. For instance, the changes to white-matter integrity caused by repeated head trauma may be amenable to detection using diffusion tensor magnetic resonance imaging.[43] Magnetic resonance spectroscopy may be capable of detecting changes

in glutamate/glutamine, N-acetyl aspartate, and myo-inositol, molecular abnormalities that may serve as markers of brain damage caused by head injuries.[44] Further, measuring tau and phospho-tau in cerebrospinal fluid may yield diagnostically useful markers of CTE.[45]

Risk and Protective Factors

CTE research is in its infancy, and decades of research are probably necessary to achieve CTE diagnosis early in its course using a combination of clinical tools and biomarkers. However, the research already conducted has profound implications for current practice by medical professionals, athletic trainers, and related specialists, as well as policy makers in government and athletic organizations. CTE is the only known neurodegenerative dementia with a specific identifiable cause; in this case, head trauma. It is unknown whether a single blow to the head is sufficient to initiate the metabolic cascade that precedes the clinical and neuropathologic changes characteristic of CTE, because all confirmed cases of CTE to date have had a history of multiple head injuries. Therefore, the most obvious way to prevent CTE is, in theory, to prevent repetitive head injuries from occurring. In some sports, such as boxing and American football, it may be impossible to prevent repetitive head injuries, especially the repeated subconcussive blows that are characteristic of the impacts felt by offensive and defensive linemen in football on nearly every play. For sports in which repeated blows to the head are unavoidable, proper concussion assessment and management may be paramount for preventing long-term consequences. Currently, it is unknown whether returning to play while symptomatic from a previous concussion or sustaining a second concussion while symptomatic is a risk factor of developing CTE. However, other strategies to reduce the number and severity of head traumas are possible, such as limiting full-contact practices, implementing rules of play that diminish the likelihood of repeated head trauma (eg, removing the 3-point stance in football), or increasing the use of newer protective headgear aimed at absorbing force, thus diminishing the impact to the brain.

Along these lines, many potential variables surrounding head trauma in athletes may be important for preventing CTE later in life. The sport played and the position played within each sport may be relevant; for instance, boxers receive a greater proportion of rotational forces to the head, whereas American football players receive a greater proportion of linear forces to the head.[46] Even within the same sport, athlete exposure to head injuries can differ considerably. In American football, some positions, such as wide receiver, may receive occasional severe blows with the potential to cause unconsciousness, whereas other players, such as linemen, may take hundreds of small impacts per season, most of which are not, by themselves, forceful enough to cause symptoms.[47] It is unknown whether CTE is more likely to occur after a small number of severe head injuries, a large number of subconcussive injuries, or other forms of head trauma. Currently, investigations are ongoing that attempt to quantify the force of head impacts across different sports and positions.[48] These findings will play an important role in understanding the specific head injury variables that influence CTE risk.

The age at which athletes suffer their head injuries may also influence CTE risk. At younger ages, the brain may be more vulnerable to injury.[49] Conversely, the increased plasticity of the young brain may be better able to compensate for specific difficulties, such as behavioral dysfunction.[50] It is also not clear whether particular lifestyle factors may be protective against CTE in the context of repetitive head injuries. In other neurodegenerative diseases such as AD, the neuropathology is thought to precede the clinical symptoms, possibly by several decades.[51] The same may be true of CTE, as

evidenced by the presence of CTE neuropathology in asymptomatic individuals studied at autopsy. Conceivably, health and medical factors that are absent or present during this preclinical stage may influence the extent of neurodegeneration or the brain's ability to compensate for any neurodegeneration. For instance, the presence of chronic inflammation, as in that which accompanies medical conditions such as obesity, hypertension, diabetes mellitus, atherosclerosis, and heart disease, may facilitate neurodegeneration and NFT formation.[52–55] Also, as with other neurodegenerative diseases like AD, some individuals may have greater *cognitive reserve*, thus increasing the threshold for the clinical manifestation of the underlying neuropathologic condition.

Genetic variations may also play an important role in moderating the relationships between head trauma, neuropathologic changes, and disordered cognition and behavior. One of the genes thought to influence CTE risk is the apolipoprotein E (APOE) gene. The APOE ε4 allele, important in the genetics of AD, may also increase the risk of CTE. Based on genetic testing conducted in conjunction with neuropathologic examinations of individuals with a history of repeated head injuries, approximately 57% of individuals with neuropathologically confirmed CTE possessed at least one APOE ε4 allele. When contrasted with the estimated 28% of the population possessing at least one APOE ε4 allele,[56] the frequency of this allele in those with CTE seems higher than expected. This genetic link is currently speculative, because formal epidemiologic studies have yet to be conducted. However, individuals carrying the APOE ε4 allele may be more likely to have a poor outcome after TBI, especially in individuals younger than 15 years.[57–59] Epidemiologic data have also implicated the APOE ε4 genotype as a risk factor for the development of AD after TBI,[60,61] and carriers of the APOE ε4 allele were found to be at increased risk of Aβ deposition after TBI.[62]

SUMMARY

CTE is a neurodegenerative disease that occurs later in the lives of some individuals with a history of repeated head trauma. The exact relationship between repetitive mild TBI, with or without symptomatic concussion, and CTE is not entirely clear, although it is possible that repetitive axonal injury sets up a series of metabolic, ionic, and cytoskeletal disturbances that trigger a pathologic cascade, leading to CTE in susceptible individuals. CTE has been reported in association with American football, professional wrestling, soccer, and hockey, as well as in association with physical abuse, epilepsy, and head banging behaviors, suggesting that mild TBI of diverse origin is capable of instigating CTE. CTE often manifests in midlife and produces clinical symptoms of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, and irritability, as well as parkinsonian signs. The characteristic neuropathologic features of CTE include extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature and widespread TDP-43-immunoreactive inclusions that may occasionally be associated with symptoms of motor neuron disease. Currently, neuropathologic examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression and to develop therapies to slow or reverse its course. Longitudinal research efforts are underway to shed additional light on the specific variables related to head trauma, neuropathology, and clinical presentation of CTE that remain in question.

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EXHIBIT 12

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Clinical presentation of chronic traumatic encephalopathy

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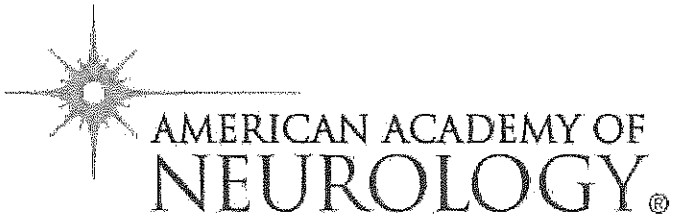

Clinical presentation of chronic traumatic encephalopathy

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ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. *Neurology*® 2013;81:1122–1129

GLOSSARY

AD = Alzheimer disease; **CSTE** = Center for the Study of Traumatic Encephalopathy; **CTE** = chronic traumatic encephalopathy; **p-tau** = hyperphosphorylated tau; **RBT** = repetitive brain trauma; **TBI** = traumatic brain injury.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau).[1,2] To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to explosive blast, and others subjected to repetitive brain trauma (RBT), including concussive and subconcussive injuries.[3–5] All reported neuropathologically confirmed cases of CTE have had exposure to RBT. However, not all individuals with histories of RBT develop CTE, indicating that additional risk factors, including genetics, likely have a role in the neuropathogenesis of this disease. For example, it has been suggested that the *APOE* ε4 allele may increase susceptibility for CTE.[6]

Previously published descriptions of the clinical presentation of CTE vary. Case reports of presumptive CTE (formerly termed dementia pugilistica or "punch-drunk" when thought limited to boxers[4]) indicated a constellation of clinical features, including impairments in cognition, behavior, and mood, and in some cases, chronic headache and motor and cerebellar dysfunction. Several case reports of boxers suggested 2 forms of presentation: 1) younger onset, with initial behavioral and mood disturbance, but with minimal cognitive and motor features; and 2) older onset, with greater cognitive impairment and, often, motor disturbance.[4,7–10] In advanced cases,

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CTE is associated with dementia, although it is unclear whether the clinical presentation of CTE dementia is different from that associated with Alzheimer disease (AD) or other age-related neurodegenerative disorders.[11–13] Herein, we describe the clinical presentation, course, and *APOE* genotype of a sample of 36 athletes with neuropathologically confirmed CTE.

METHODS Subjects. The brains of 81 subjects in the Boston University Center for the Study of Traumatic Encephalopathy (CSTE) brain bank met recently published criteria for the neuropathologic diagnosis of CTE.[1] For the current study, 45 cases were excluded because of 1) primary exposure to RBT from nonathletic activities; 2) inability to contact next-of-kin to conduct an interview; and 3) presence of comorbid motor neuron disease,[14] neurodegenerative disease, or other significant neuropathology. Seven were military veterans with unknown or no athletic history, 10 had no next-of-kin contact, and 28 had comorbid neuropathologic disease. Of the 36 remaining subjects, 28 were included in a previous report[1] and 8 were new cases.

CTE neuropathologic staging. The cases were categorized into the 4-stage rating scale of CTE (I = least severe, IV = most severe) based on the severity of p-tau pathology, as previously reported.[1] Diagnosis and staging were conducted blind to medical history, *APOE* genotype, and informant interview.

Interview and medical record review. History and clinical presentation were obtained through postmortem telephone interviews with next-of-kin by a neuropsychologist (R.A.S.) blinded to neuropathologic findings and *APOE* genotype status. Medical records were available and reviewed for 23 cases. The semistructured interview was based on previous studies of postmortem dementia diagnosis made by interviews with family members.[15,16] Information queried during the interview included the following: demographics; cause of death; and athletic, military, medical, neuropsychiatric, and social/occupational histories. The interview included specific questions regarding dementia, depression, changes in cognition, behavior, mood, and motor functioning, as well as instrumental activities of daily living. Responses were qualitatively summarized into an overall assessment of the subject's presentation and course of symptoms and functioning. The number of informants interviewed per case ranged from 1 to 7 (median = 2), with each interview lasting approximately 60 minutes. Interviews were conducted at a median time of 4 months after time of death.

***APOE* genotyping.** DNA was extracted from brain tissue samples using a Qiagen QIAamp DNA extraction kit (Qiagen, Valencia, CA). Two single nucleotide polymorphisms (National Center for Biotechnology Information SNPs rs429358 and rs7412) were examined using TaqMan assays (Applied Biosystems, Foster City, CA). Allelic discrimination was automated using the manufacturer's software. Positive controls, consisting of DNA of each of the 6 possible *APOE* genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), were included on each plate and genotyped with restriction isotyping.

Statistical analyses. Between-group differences were examined by independent sample *t* tests. Chi-square analyses were used for between group comparisons for categorical data. *APOE* genotype analyses comparing CTE cases with population norms[17] were conducted with the χ^2 goodness-of-fit test. A probability level of $p = 0.05$ was used throughout. All statistical analyses were conducted with IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY).

Standard protocol approvals, registrations, and patient consents. Approvals for brain donation, postmortem clinical record review, interviews with family members, and neuropathologic evaluation were provided by the Institutional Review Boards of Boston University Medical Center and the Bedford VA Hospital.

RESULTS Table 1 summarizes the demographics, cause of death, athletic history, neuropathologic stage, and *APOE* genotypes of the sample. All subjects were male athletes, with 6 (17%) African American and 1 (3%) of Hispanic origin. There were 29 football players (22 who played professionally, 4 who only played through college, and 3 who only played through high school), 3 professional hockey players, 1 professional wrestler, and 3 boxers (1 professional, 2 amateur). Of the football players, the most common position played was lineman (48%), followed by running back (21%), linebacker (10%), and smaller numbers of other positions. There were no quarterbacks or kickers. Of the 36 subjects, 3 (8%) were asymptomatic. Tables 2 and 3 describe the clinical features and course of the remaining 33 subjects.

Eleven of the symptomatic cases were reported to have initial changes in cognitive functioning (e.g., episodic memory impairment, executive dysfunction) before behavioral or mood disturbance. Initial changes in behavior (e.g., explosivity, impulsivity, violence) before mood or cognitive disturbance were reported in 13 subjects. Mood changes (e.g., depression, hopelessness) were reported as the initial feature in 9 subjects. None of the subjects had motor disturbance as their initial feature. The subgroups with initial behavioral symptoms and mood changes were similar in age of initial presentation, age of death, and neuropathologic stage, and were combined into a behavior/mood group (n = 22). Subjects whose initial difficulties involved cognitive functioning comprised a cognition group (n = 11). Tables 1–3 describe demographics and clinical features for the behavior/mood and cognition subgroups.

Ten subjects were diagnosed with dementia; 4 were clinically diagnosed with AD, 4 with "dementia pugilistica" or "football-related" dementia, and 2 with unspecified dementia. All had stage IV CTE. Of the 10, 7 exhibited cognitive symptoms initially, 2 exhibited mood symptoms initially, and 1 initially presented with behavior changes. The mean age of symptom onset for the dementia group was 57.7 years (SD = 18.3; range 25–82) and the mean age of dementia diagnosis was 72.6 years (SD = 8.5, range 56–83). The mean length of time between dementia diagnosis and death was 8.0 years (SD = 5.5, range <1–15). Four subjects with dementia had gait difficulties, 3 had

Table 1 Description of sample by initial clinical presentation

Variable	All subjects (n = 36)	Behavior/mood group (n = 22)[a]	Cognition group (n = 11)[a]
Age at death, y, mean ± SD (range)	56.8 ± 21.9 (17–98)	51.4 ± 18.5 (21–84)[b]	69.2 ± 21.8 (34–98)[b]
Cause of death, %			
Systemic illness	41.8	49.8	27.3
Accidental overdose	13.9	18.2	9.1
Dementia-related	13.9	9.1	27.3
Suicide	16.7	18.2	18.2
Injury	8.4	4.5	18.2
Years of education, mean ± SD (range)	15.0 ± 2.4 (10–20)	14.5 ± 2.4 (10–18)	15.7 ± 1.4 (13–18)
Football as primary sport, %	80.6	72.7	90.9
Total years of football played, mean ± SD (range)	15.3 ± 6.4 (3–25)	14.4 ± 6.5 (3–25)	18.2 ± 5.9 (5–24)
Neuropathologic severity stage, %			
Stage I	8	9.1	0
Stage II	28	31.8	9.1
Stage III	31	31.8	36.4
Stage IV	33	27.3	54.5
APOE genotype,[c] %			
ε2/ε2	0	0	0
ε2/ε3	3	4.5	0
ε2/ε4	0	0	0
ε3/ε3	63	63.6	54.5
ε3/ε4	26	27.3	27.3
ε4/ε4	9	4.5	18.2

[a] Three subjects were asymptomatic; percentages within initial feature group are based on the percent of symptomatic subjects.
[b] Statistically significant between-group difference, $p < 0.05$.
[c] One subject did not have *APOE* genotyping.

a history of falls, and 1 had a history of tremor. Two subjects (20%) with dementia had a history of headaches, compared with 11 subjects (44%) without dementia. All 10 subjects had both memory and executive impairment, 7 had language deficits, and 2 had visuospatial difficulties. Six of the 10 were characterized by behavioral impairment, predominantly described as having a "short fuse" or being "out of control." Four of the 10 were physically violent and 2 were verbally violent. Although one subject demonstrated disinhibited behavior, none of the subjects had disinhibited speech or socially inappropriate behaviors. Of the 7 who were reported to have mood disturbance, 2 had predominantly sadness/depressive symptoms and 2 had anxiety symptoms. The only 2 subjects in the entire sample reported to have had apathy were in the dementia group.

The proportions of *APOE* genotypes (i.e., ε4 homozygotes, combined ε4 homozygotes and heterozygotes, and ε4 noncarriers) in our CTE sample were significantly different from those found in an age-matched normative sample[17] (χ^2 [2] = 6.63, $p < 0.05$). A binomial test revealed that the primary difference between our CTE sample and population norms was a greater proportion of ε4 homozygotes in our sample ($p < 0.05$). When examining the 2 initial presentation groups, there were no differences between the behavior/mood group and the age-matched normative sample (χ^2 [2] = 0.46, $p > 0.05$). However, there were proportionally more ε4 homozygotes in the cognition group than expected (χ^2 [2] = 13.3, $p < 0.05$). The relative proportions of *APOE* genotypes in our 10 subjects with dementia were not significantly different from those seen in AD[18] (χ^2 [2] = 1.52, $p > 0.05$).

DISCUSSION Consistent with earlier reports of boxers,[4,7–10] our findings suggest that there may be 2 different clinical presentations of CTE, with one initially exhibiting behavioral or mood changes, and the other initially exhibiting cognitive impairment. The behavior/mood group demonstrated symptoms at a significantly younger age than the cognition group. Although almost all subjects in the behavior/

Table 2 Clinical features and course by initial clinical presentation

Variable	All symptomatic subjects (n = 33)[a]	Behavior/mood group (n = 22)[a]	Cognition group (n = 11)[a]
Percent with progressive course	90.9	86.4	100
Percent with dementia diagnosis at death	30.3	18.2[b]	54.5[b]
Age first clinical feature observed, y, mean ± SD (range)	42.5 ± 17.8 (19–82)	34.5 ± 11.6 (19–59)[b]	58.5 ± 17.7 (31–82)[b]
Duration of clinical features, y, mean ± SD (range)	14.9 ± 12.9 (0–51)	17.0 ± 14.3 (0–51)	10.7 ± 8.5 (1–30)
Initial clinical domain, %			
Cognition	33.3	—	100
Behavior	39.4	59.1	—
Mood	27.3	40.9	—
Clinical domain(s) ever observed during life, %			
Cognition	93.9	90.9	100
Behavior	75.8	86.4[b]	54.5[b]
Mood	84.8	95.4[b]	63.6[b]
Motor	30.3	27.3	36.4
Cognition and behavior	75.8	86.4	54.5
Cognition and mood	81.8	90.9	63.6
Cognition and motor	30.3	27.3	36.4
Behavior and mood	72.7	86.4	45.5
Behavior and motor	27.3	27.3	27.3
Mood and motor	30.3	27.3	36.4
Cognition, behavior, and mood	72.7	86.4	45.5
Cognition, behavior, and motor	27.3	27.3	27.3
Cognition, mood, and motor	30.3	27.3	36.4
Behavior, mood, and motor	27.3	27.3	27.3
All 4 domains	27.3	27.3	27.3
History of significant headaches, %	34.4	38.1	27.3
Death by suicide, %	18.2	18.2	18.2
History of substance abuse, %	39.4	36.4	45.5

[a] Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.
[b] Statistically significant, $p < 0.05$.

mood group demonstrated cognitive impairments at some point, significantly fewer subjects in the cognition group demonstrated behavioral and mood changes during the course of their illness. There were distinctions between the 2 groups regarding specific features present in each domain. The behavior/mood group was significantly more explosive, out of control, physically and verbally violent, and depressed than the cognition group. Whereas all subjects in the cognition group were reported to have impaired episodic memory, approximately one-quarter of the behavior/mood group did not have memory difficulties. Subjects in the cognition group were significantly more likely to progress to dementia than those in the behavior/mood group but were also significantly older at the time of death. Given the small sample size in this study, however, it is unclear whether these 2 apparently distinct clinical subtypes are representative of all individuals with CTE. In addition, the subsample of cases with dementia is also small, thus limiting the generalization of the presentation of CTE dementia. Further research is needed to clarify and validate these findings.

We examined the potential role of the *APOE* ε4 allele as a susceptibility factor for CTE. Our findings indicate that there were significantly more ε4 homozygotes in the sample than expected in a normal, age-matched population. Furthermore, this effect was largely driven by the cognition group: 2 of 11 subjects in the cognition group and 1 of 22 subjects in the behavior/mood group were homozygous for the ε4 allele. In addition, 1 of the 10 CTE subjects diagnosed

Table 3 Specific clinical features by initial clinical presentation

Variable	All symptomatic subjects, % (n = 33)	Behavior/mood group, % (n = 22)[a]	Cognition group, % (n = 11)[a]
Cognitive features			
Memory impairment	84.8	77.3	100
Executive dysfunction	78.8	72.7	90.9
Attention and concentration difficulties	72.7	63.6	90.9
Language impairment	57.6	54.5	63.6
Visuospatial difficulties	54.5	54.5	54.5
Behavioral features			
Explosivity	57.6	72.7[b]	27.3[b]
Impulse control problems	45.5	54.5	27.3
"Out of control"	51.5	63.6[b]	27.3[b]
Physically violent	51.5	68.2[b]	18.2[b]
Verbally violent	48.5	73.6[b]	18.2[b]
Disinhibited speech	0	0	0
Disinhibited behavior	3.0	0	9.1
Socially inappropriate	3.0	0	9.1
Paranoia	18.2	22.7	9.1
Mood features			
Sadness/depression	63.6	86.4[b]	18.2[b]
Anxiety/agitation	15.2	13.6	18.2
Manic behavior/mania	3.0	4.5	0
Suicidal ideation/attempts	30.3	31.8	27.3
Hopelessness	63.6	72.7	45.5
Apathy	6.1	9.1	0

[a] Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.
[b] Statistically significant between-group difference, $p < 0.05$.

with dementia during life was ε4 homozygous. Although interpretation and generalization of these results is difficult because of the small sample, the proportion of ε4 homozygosity is in contrast to population norms in which ε4 homozygosity only occurs in 1% to 3% of the general population,[17] and more consistent with the 10% of patients with AD who are ε4 homozygous.[18] The *APOE* ε4 variant is the largest known genetic risk factor for sporadic AD.[18] It has been associated with β-amyloid, but not tau, deposition in cognitively normal aging.[19] *APOE* ε4 has also been associated with greater severity of cognitive deficits and longer recovery time after traumatic brain injury (TBI) and RBT in a variety of populations, including boxers and professional football players,[20–24] and may increase the risk of clinical dementia after TBI.[25] It has been hypothesized that the *APOE* ε4 isoform may have direct neurotoxic effects leading to mitochondrial dysfunction and cytoskeletal changes, resulting in increased risk of neurodegeneration.[26] Despite the small sample size and other limitations in the current study, future research on the role of *APOE* in CTE risk appears warranted. However, other potential susceptibility genes also merit consideration, including mutations to the microtubule-associated protein tau (*MAPT*) gene, the progranulin (*GRN*) gene, and the chromosome 9 open reading frame 72 (*C9ORF72*) gene. Moreover, additional nongenetic risk factors for CTE should be examined in future research, including studies to determine what specific aspects of RBT exposure (e.g., types, severity, frequency, initial age, and duration of trauma) are associated with CTE, as well as what potential lifestyle variables (e.g., diet, exercise, obesity, steroid use) are associated with the disease initiation and variability in presentation.

It is noteworthy that motor features, including parkinsonism, were not common in our sample. This is in contrast to some earlier descriptions of CTE in boxers, in which these motor features were quite prominent.[4] However, our findings are consistent with other case reports of predominantly younger onset boxers, in which motor disturbance was not common.[4,7–10] It is not clear why some individuals with CTE develop motor features and others do not. One possibility may be the differences in the biomechanics of injury. For example, in boxing, angular acceleration and torsional injury involving the brainstem and cerebellum is thought to be a pathogenic mechanism of TBI after a hook or jab to the jaw, whereas transverse and linear acceleration and deceleration injury are more characteristic of football dynamics.[27,28] As a result, degeneration of brainstem structures that produce parkinsonism, such as the substantia nigra, might occur earlier in the course of disease in boxers. In contrast, football players might develop substantia nigra degeneration later in the course of their disease, at a time when widespread cortical and basal ganglionic degeneration mask the development of motor disturbance. Related mechanisms of injury leading to CTE have been suggested by recent experimental studies of blast neurotrauma.[3]

Although many of the symptoms of CTE are similar to AD and other causes of dementia,[11,29] there are factors that appear to clinically differentiate CTE from other age-related neurodegenerative diseases. For example, behavioral changes observed early in the course of CTE could be confused with the behavioral variant of frontotemporal dementia, especially in a patient in his or her 50s without any significant memory impairment. However, common changes in the behavioral variant of frontotemporal dementia typically include disinhibited and inappropriate behavior and speech, as well as apathy[30]; these symptoms were not frequent in our case series. In addition, the progressive memory impairment observed in more than 80% of our CTE cases, and in all 10 of

the subjects with dementia, could lead to an inaccurate diagnosis of AD when the underlying disease is CTE.[12]

It is not clear what neuropathologic changes may lead to the 2 possible clinical presentations observed in this study. It is unlikely that the small, focal cortical p-tau lesions found in stage I and II CTE produce clinically meaningful behavioral and mood symptoms. However, these features may be associated with the neurofibrillary tangles in the locus coeruleus and amygdala found in younger subjects in a previous report.[1] The memory and executive dysfunction in the older cognition group may be due to the more extensive degenerative changes in the hippocampus and frontal cortices seen in CTE stages III and IV.[1] It is possible, however, that some of the features evident in the younger behavior/mood group were due to persistent postconcussion syndrome,[31] with unresolved or even progressive[32] axonal damage resulting from the initial traumas. Axonal injury has been shown in all neuropathologic stages of CTE, ranging from multifocal, perivascular axonal varicosities in the cortex and white matter in stages I and II, to more extensive, diffuse axonal loss in the cortex and white matter in stages III and IV.[1] Recent reports have demonstrated that repetitive subconcussive trauma is associated with white matter abnormalities on diffusion tensor imaging[33,34] and abnormal functional MRI tests.[35] Additional findings indicate that there may be persistent and progressive inflammation and white matter degeneration after even a single TBI.[36] Further research is required to delineate these clinicopathologic relationships.

Three subjects in our case series were asymptomatic. One of these cases was only 17 years old and had stage I neuropathology. Both of the other 2 cases were much older football players (one in 40s, one in 80s), had stage II neuropathology, and were homozygous for *APOE* ε3. Both also had advanced graduate degrees, were very successful in their professional careers, and were described as extremely intelligent. Although speculative, these findings raise the possibility that cognitive reserve[37] may have a role in protecting against the clinical manifestations of CTE. A recent report suggests that cognitive reserve may mitigate cognitive decline in older individuals with earlier life TBI.[38] Future research examining the roles of cognitive reserve, genetics, and environmental factors in determining resilience to clinical manifestations and the progression of p-tau pathology will help elucidate the pathobiology of CTE.

Although these findings are based on the largest cohort of subjects with neuropathologically confirmed CTE without comorbidities studied to date, interpretation and generalizability of these results are limited by several factors. First, the overall sample size is small, and caution should be taken when generalizing these results to the larger population of athletes or to the overall clinical presentation of CTE. In addition, there are inherent selection biases imposed in a postmortem brain donation study. For example, families choosing to donate may be more likely to have witnessed symptoms during life. This could lead to reports of more severe symptoms than a typical CTE population, and could account for only having 3 asymptomatic cases. From the broader CTE cohort in the CSTE brain bank, we selected a smaller sample by eliminating individuals with comorbid pathology and only including athletes; this restriction may further limit the generalizability of our findings. Results from this study should not be interpreted in terms of population prevalence or generalized to living athletes with CTE. In addition, there is the potential for reduced reliability and validity of retrospective reports from family members after the death of a loved one. However, several studies have demonstrated adequate reliability and validity of these verbal autopsies in a variety of patient populations, including those with dementia[15,16] and psychiatric disorders.[39] There also may be differences in the accuracy of informant reports when comparing younger and older subjects. That is, informants of older subjects were asked to recall early- or midlife events possibly resulting in reduced accuracy compared with the informants of younger subjects. Finally, there was no comparison group of former athletes without CTE. This may limit the ability to draw conclusions that the clinical presentation described is specifically due to the effects of CTE. In our available dataset of subjects whose tissue had been examined at the BU CSTE brain bank, there was not an adequate number of subjects without CTE to make such a comparison. For example, 34 of 35 former professional football players had neuropathologically confirmed CTE.[1] Future research is needed to clarify the clinical presentation of CTE. The development of biomarkers (e.g., blood, CSF, neuroimaging, and tau-specific radiotracers) will result in the ability to detect and diagnose CTE during life and subsequent studies of risk factors, epidemiology, and treatment.[40]

AUTHOR CONTRIBUTIONS

Dr. Stern was responsible for drafting the manuscript, study concept and design, and analysis and interpretation of data. He also conducted some of the statistical analyses and had a role in obtaining funding. Mr. Daneshvar participated in drafting the manuscript, as well as acquisition of data, statistical analysis, and interpretation of data. Ms. Baugh participated in drafting the manuscript, as well as study design and acquisition of data. Dr. Seichepine participated in drafting the manuscript, as well as analysis and interpretation of data. Mr. Montenigro participated in drafting the manuscript and in study design. Mr. Riley participated in revising the manuscript, study design, and acquisition of data. Mr. Fritts, Ms. Stamm, Mr. Robbins, and Ms. McHale participated in revising the manuscript and acquisition of data. Ms. Simkin participated in revising the manuscript as well as conducting the *APOE* genotyping. Dr. Stein and Dr. Alvarez participated in revising the

manuscript, as well as acquisition and analysis of neuropathologic data. Dr. Goldstein and Dr. Budson participated in revising the manuscript and interpreting the data. Dr. Kowall participated in revising the manuscript, interpreting the data, and obtaining funding. Mr. Nowinski participated in revising the manuscript, study concept, acquisition of data, and obtaining funding. Dr. Cantu participated in drafting the manuscript, study design and concept, interpreting data, and obtaining funding. Dr. McKee participated in drafting the manuscript, study design and concept, acquiring, analyzing, and interpreting clinical data, acquiring, analyzing, and interpreting the neuropathologic data, and obtaining funding.

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